Catalytic Formal Homo-Nazarov Cyclization

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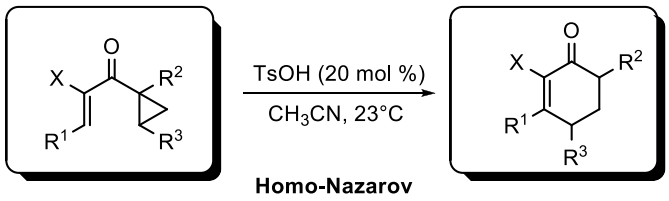
ABSTRACT



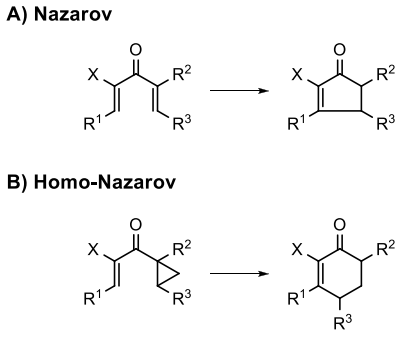
The first catalytic method for the cyclization of vinyl-cyclopropyl ketones (formal homo-Nazarov reaction) is reported. Starting from activated cyclopropanes, heterocyclic and carbocyclic compounds were obtained under mild conditions using Brønsted acid catalysts. Preliminary investigation of the reaction mechanism indicated a stepwise process.

Carbocyclic and heterocyclic scaffolds occupy a privileged position in both natural products and pharmaceuticals.[1] Consequently, the development of cyclization and cycloaddition reactions for the efficient formation of cyclic structures is a very important goal in organic chemistry. In this respect, the development of new, highly stereoselective catalytic methods is crucial to allow a more efficient and environmentally friendly access to polycyclic molecules.[2]

One classical approach towards the construction of cyclopentenone rings is the Nazarov reaction, which is the electrocyclic ring closure of a pentadienyl cation, followed by proton transfer (**A**, Scheme 1).[3] The potential of the Nazarov cyclization was recognized at an early stage in organic synthesis. Solutions to control the termination of the reaction were devised several decades ago,[3b] but the necessity of using a stoichiometric amount of strong Lewis or Brønsted acids has limited the use of this reaction. However, in the last five years the first examples of catalytic Nazarov reactions using milder Lewis[3c-3n] or Brønsted[3o,3p] acids were reported, together with the first examples of asymmetric induction.[3e,3k,3l,3n, 3o]

(1) Clardy, J.; Walsh C. *Nature* **2004**, *432*, 829.
(2) (a) Balskus, E. P.; Jacobsen, E. N. *Science* **2007**, *317*, 1736. (b) Mohr, J. T.; Krout, M. R.; Stoltz, B. M. *Nature* **2008**, *455*, 323.
(3) (a) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR. Ser. Khim.* **1941**, 211. (b) Habermas, K. L.; Denmark, S. E.; Jones, T. K.; *Org. React. (N. Y.)* **1994**, *45*, 1-158. (c) Giese, S.; West, F. G. *Tetrahedron* **2000**, *56*, 10221. (d) Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett.* **2003**, *5*, 2747. (e) Aggarwal, V. K.; Beffield, A. J. *Org. Lett.* **2003**, *5*, 5075. (f) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927. (g) He, W.; Sun, X. F.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278. (h) Janka, M.; He, W.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 6864. (i) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (j) He, W.; Herrick, I. R.;. Atesin, T. A; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003. (k) Liang, G. X.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931. (l) Liang, G. X., Trauner D. *J. Am. Chem. Soc.* **2004**, *126*, 9544. (m) Walz, I.; Bertogg, A.; Togni, A. *Eur. J. Org. Chem.* **2007**, 2650. (n) Walz, I.; Togni, A. *Chem. Commun.* **2008**, 4315. (o) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097. (p) Amere, M.; Blanchet, J.; Lasne, M. C.; Rouden, J. *Tetrahedron Lett.* **2008**, *49*, 2541. For reviews, see: (q) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193. (r) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (s) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479.

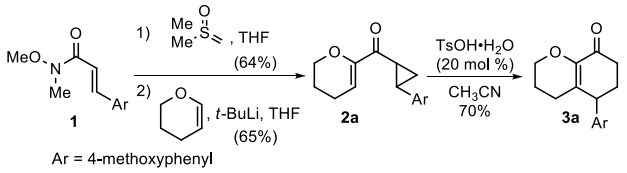
Scheme 1. Nazarov and Homo-Nazarov Cyclizations



When considering these recent successes in the Nazarov reaction, we wondered if similar concepts could be successful in other cyclization reactions to access larger ring systems. A viable approach to access homologous rings via electrocyclic reactions is the substitution of a double bond by a cyclopropyl group, as exemplified by the divinylcyclopropyl rearrangement.[4] Intra- and intermolecular ring-opening of cyclopropyl ketones and diesters have been examined extensively.[5] The reaction of vinyl-cyclopropyl ketones has been less studied (**B**, Scheme 1).[6] Tsuge has reported the cyclization of vinyl-cyclopropyl ketones using an excess of polyphosphoric acid at 80°C, but this reaction was not general and several other products were obtained beside the desired cyclohexenones.[6a] More work has been done on the related aryl-cyclopropyl ketones, first by Murphy for the synthesis of tetralones using an excess of $SnCl_4$ as reagent.[6b-6d] During completion of our work, Yadav also demonstrated that diverse polycyclic heterocycles could be accessed using 3 equivalents $SnCl_4$ at 80°C, but no vinyl-cyclopropyl ketones were reported.[6e] Up to now, the harsh conditions needed have limited the use of the homo-Nazarov reaction in organic synthesis. Herein, we report the first example of a catalytic formal homo-Nazarov process for non aromatic substrates which lead to the formation of valuable polycyclic cyclohexenones at room temperature as well as preliminary experiments to probe the reaction mechanism.

Inspired by recent progress in the catalytic Nazarov reaction,[3j] we decided to examine dihydropyran-derived substrate **2a** (Scheme 2). Substrate **2a** was synthesized from Weinreb amide **1** via Corey-Chaykovsky cyclopropanation[7] followed by addition of a lithiated nucleophile to afford **2a** in good yield (Scheme 2).

Scheme 2. Synthesis and Cyclization of Model Substrate **2a**.



With our model substrate in hand, we began our studies by examining the most frequently used procedure for homo-Nazarov cyclization: stoichiometric $SnCl_4$.[6b-6e] Using these conditions, complete polymerization of the sensitive substrate was observed.[8]

As most Lewis acid led to extensive polymerization, we then turned towards Brønsted acid catalysts. The pK_a value of the catalyst had a strong influence on the outcome of the reaction: Sulfuric and toluenesulfonic acids were optimal. Stronger acids led to decomposition of the starting material and no full conversion could be achieved with weaker acids. Examination of solvent effects showed that the reaction was faster in non-coordinating solvents, like dichloromethane, but polymerization was also difficult to suppress. Acetonitrile finally offered the best compromise, with sufficient reactivity but less pronounced polymerization. The cyclization of **2a** in acetonitrile with 20 mol % toluenesulfonic acid at room temperature led to the formation of the desired cyclohexenone **3a** in 70% isolated yield (Scheme 2).

The scope of the reaction was examined next (Table 1). Variation of the aromatic substituent on the cyclopropane confirmed the importance of its electron-donating ability: whereas no reaction was observed with a simple phenyl group (entry 2), a quantitative yield was observed with a 3,4- or 2,4- dimethoxyphenyl group (entries 3 and 4). This result is noteworthy, as electron-rich aromatic substituents are well represented in bioactive natural products[9] and are easily oxidized to the corresponding carboxylic acids.[10] A furan group was also tolerated at this position, although the yield was moderate due to partial polymerization (entry 5).

Finally, the influence of a methyl group α to the ketone was examined. Interestingly, a strong accelerating effect

(4) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 5, p 971-998.

(5) For a few selected examples, see: (a) Stork, G.; Marx, M. *J. Am. Chem. Soc.* **1969**, 91, 2371. (b) Grieco, P. A.; Finkelhor, R. S. *Tetrahedron Lett.* **1974**, 527. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, 130, 8642.

(6) (a) Tsuge, O.; Kanemasa, S.; Otsuka, T.; Suzuki, T. *Bull. Chem. Soc. Jpn.* **1988**, 61, 2897. (b) Murphy, W. S.; Wattanasin, S. *Tetrahedron Lett.* **1980**, 21, 1887. (c) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2920. (d) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc. Perkin Trans. 1* **1982**, 1029. (e) Yadav, V. K.; Kumar, N. V. *Chem. Commun.* **2008**, 3774.

(7) Rodriques, K. E. *Tetrahedron Lett.* **1991**, *32*, 1275.

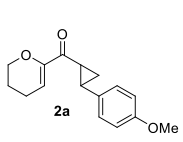
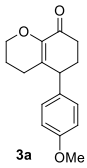
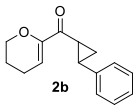
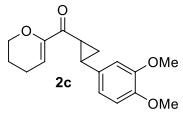
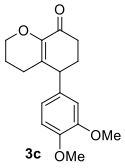
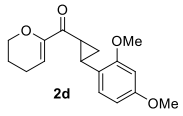
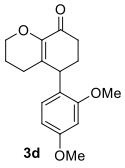
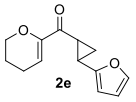
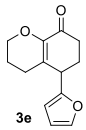
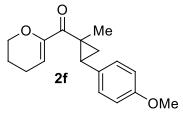
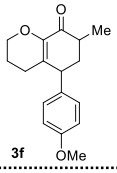
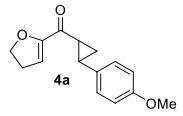
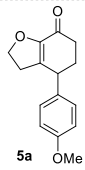
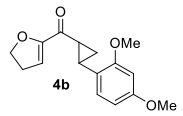
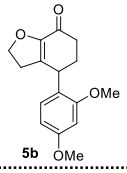
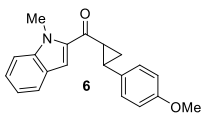
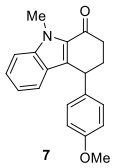
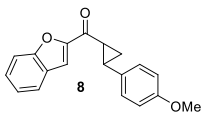
(8) Oligomerization, then polymerization was apparent in ^{1}HNMR via formation of broad signals in several regions of the spectra, see Supporting Information (Figure S5).

(9) For example in Podophyllotoxin natural products and their derivatives: Bohlin, L.; Rosen, B. *Drug Discov. Today* **1996**, *1*, 343.

(10) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Voight, E. A.; Rein, C., Burke, S. D. *J. Org. Chem.* **2002**, *67*, 8489.

was observed and cyclohexenone **3f** was obtained in quantitative yield after only 15 min (entry 6).

Table 1. Scope of the formal homo-Nazarov Cyclization

entry	substrate	product	isolated yield[a] reaction time
1			70% 18 h
2		-	No Reaction
3			quant 5 h
4			quant 15 min
5			50% 3h
6			quant (dr = 5:1) 2 h
7			15% 36 h
8			quant 1 h
9			quant 5 h
10		-	Polymerization

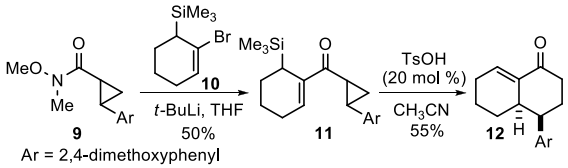
[a] Reaction conditions: 0.4 mmol substrate in 8 mL CH_3CN with 20 mol % TsOH at 23°C.

A plausible explanation would be a faster ring-opening of the cyclopropane ring due to sterical strain release and the higher stability of the formed enol intermediate.[11] Importantly, this accelerating effect on the formal homo-Nazarov cyclization has never been reported before.

We then examined variation of the electron-rich side of the ketone. A dihydrofuran group proved to be more prone to polymerization and the desired product was isolated only in low yield with a 4-methoxyphenyl group on the cyclopropane (entry 7). The stronger stabilizing effect of the 2,4-dimethoxyphenyl substituent allowed the isolation of the desired 5-6 ring system in quantitative yield (entry 8). Replacing the dihydropyran group with an electron-rich *N*-methylindole heterocycle lead to an efficient cyclization in quantitative yield (entry 9), but only polymerization was observed with a benzofuran ring (entry 10). Interestingly, similar results were obtained in the related Nazarov cyclization.[3i]

In order to further increase the versatility of the formal homo-Nazarov process, it would be important to diminish the strong electronic constraints which limit the number of structures that can be synthesized. The use of substrates lacking an electron-donating hetero atom on the double-bond is highly desirable. Based on the seminal work of Denmark on silyl group-directed Nazarov reactions,[3b,12] we decided to use an allyl silane group to enhance the nucleophilicity of the double bond and favorize cyclization (Scheme 3).

Scheme 3. Cyclization for Carbocycles Synthesis



Gratifyingly, submitting vinyl-cyclopropyl ketone **11** to the optimized reaction conditions led to the formation of bicyclic ketone **12** in 30 min and 55% yield. The regioselectivity of the double bond formation was completely controlled by the elimination of the silyl group. Interestingly, only one diastereoisomer of **12** was isolated. The structure of **12** was tentatively assigned by NMR experiments (COSY, HSQC, NOESY).[13] This preliminary result held promises for the application of the method in the synthesis of carbocyclic compounds.

The strong influence of electron-donating groups and acid strength on the reaction rate led us to propose a

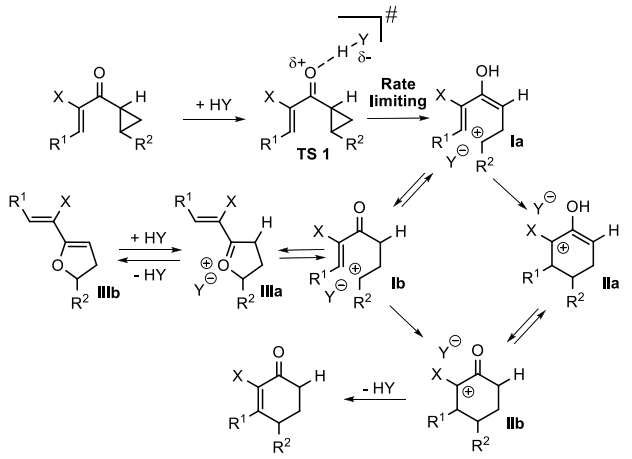
(11) As an alternative explanation, a higher fraction of the more stable enol tautomer could be envisaged to favor cyclization.

(12) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.

(13) The obtained 2D NMR data strongly support the proposed structure assignment for **12**. Further confirmation of the structure will be attempted by X-rays analysis of the corresponding thiosemicarbazone, a procedure developed by Denmark.[12]

tentative stepwise mechanism for the reaction with cyclopropane opening as rate-limiting (Scheme 4).

Scheme 4. Postulated Mechanism

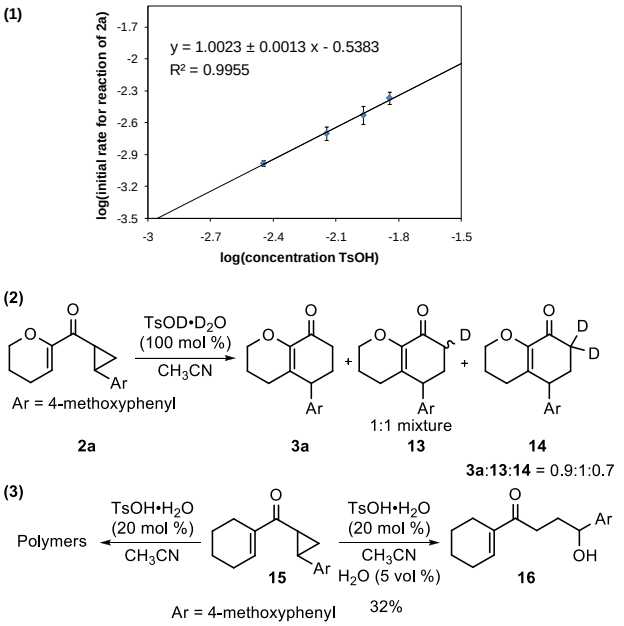


In order to further support this mechanism, the following experiments were performed (Scheme 5): (1) The reaction kinetic was followed via ^{1}H NMR spectroscopy, and the reaction was found to be first order in tosic acid for substrate **2a**. (2) The use of stoichiometric deuterated tosic acid resulted in a mixture of non-deuterated, mono and bis-deuterated products at the α position to the ketone. A control experiment showed that no deuterium exchange was observed for the isolated cyclization product in the presence of deuterated tosic acid. A possible explanation for this surprising results would be the intramolecular attack of the oxygen atom of intermediates **Ia** or **Ib** to form an oxonium intermediate **IIIa**. From **IIIa**, proton-deuterium exchange should be easy via dihydrofuran **IIIb**. Dihydrofuran products have indeed been isolated in the related stoichiometric reaction of aryl vinyl ketones.[6c] Alternatively, proton exchange could be more rapid on cyclized intermediate **IIb** and **IIa**. Proton lost form **IIb**, or proton lost followed by tautomerization from **IIa** would then lead to the cyclohexenone product. Additionally, a weak kinetic isotope effect (1.15) was observed using 40 mol % deuterated tosic acid, but this result is difficult to interpret due to fast proton exchange between substrate and catalyst. (3) Attempts were made to trap the proposed intermediates (enol and carbocation) of the catalytic cycle.[14] With substrate **2a**, all nucleophilic (water, allyl silane, butyl vinyl ether) and electrophilic (benzaldehyde, ethyl glyoxalate, acetic anhydride, ethyl acrylate) trapping agents tested so far were not successful. With cyclohexene derivative **15**, however, alcohol **16** was obtained in 31% yield when the reaction was conducted in the presence of water.

(14) To gain stronger evidence for the cationic mechanism, we will study the influence of the cyclopropane stereochemistry on the reaction outcome, for example using **11** with a *cis*-substituted cyclopropane.

All the data collected so far are in agreement with a rate-determining cyclopropane opening, followed by a fast cyclization. In the case were the cyclization is too slow (as with **15**), polymerization can occur instead of the desired process. We speculate that key for catalysis is the fast tautomerization of the enol intermediates, which contrasts with the strong binding of stoichiometric reagents like $SnCl_4$, which prevent catalytic turnover.

Scheme 5. Mechanism Investigation: (1) Van't Hoff Plot and Reaction Order (2) Deuterium and (3) Trapping Experiments



In summary, we have reported the first catalytic formal homo-Nazarov process. We have demonstrated that principles successful in the corresponding Nazarov reaction could also be applied to vinyl-cyclopropyl ketones, which allow the first high-yielding cyclization reaction for this class of substrates under mild conditions. First investigations of the reaction mechanism seem to indicate a stepwise mechanism with a rate-limiting cyclopropane ring opening: consequently, the reaction is mechanistically different from the classical Nazarov cyclization. Our future work will focus on the development of asymmetric variations as well as on applications in the synthesis of natural products and their analogs.

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Supporting Information Available Experimental procedures, spectroscopic information for new

compounds and kinetic data. This material is available free of charge via the Internet at http://pubs.acs.org

Supporting information

Catalytic Formal Homo-Nazarov Cyclization

*Filippo De Simone, Julien Andrès, Riccardo Torosantucci and Jérôme Waser**

57 pages

1 General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, *Karl-Fischer* titration). NEt_3 and pyridine were distilled under nitrogen from KOH. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar pressure.TLC was performed on Merck silica gel 60 F_{254} TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain.Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration; interpretation).^{13}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

2 General Procedures

General procedure 1: formation of Weinreb's amides

Following the reported procedure[1] *N*-methylmorpholine (1.1 equiv) was added to a solution of acid (1.0 equiv) in DMF (1 M) at 0 °C. After 25 min, *iso*-butylchloroformate (1.1 equiv) was added dropwise at 0 °C. After 10 min, *N*,*O*-dimethylhydroxylamine hydrochloride (1.1 equiv) was added, followed by *N*-methylmorpholine (1.3 equiv) and the reaction mixture was warmed to 23°C. After 6 h, the reaction was quenched with 0.5 M HCl (2 mL/mmol of acid) and extracted with CH_2Cl_2 (3x2 mL/mmol of acid). The combined organic layers were washed with 0.5 M NaOH (2x2 mL/mmol of acid), brine (2 mL/mmol of acid), dried over $MgSO_4$ and the solvent was removed under reduced pressure. After 30 min in high vacuum, the residues were dissolved in Et_2O (6 mL/mmol of acid) and washed with brine (2x3 mL/mmol of acid),

[1] Nagarajan, S. R.; Lu, H. F.; Gasiecki, A. F.; Khanna, I. K.; Parikh, M. D.; Desai, B. N.; Rogers, T. E.; Clare, M.; Chen, B. B.; Russell, M. A.; Keene, J. L.; Duffin, T.; Engleman, V. W.; Finn, M. B.; Freeman, S. K.; Klover, J. A.; Nickols, G. A.; Nickols, M. A.; Shannon, K. E.; Steininger, C. A.; Westlin, W. F.; Westlin, M. M.; Williams, M. L. *Bioorg. Med. Chem.* **2007**, *15*, 3390-3412.

dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the Weinreb amide which was used directly without purification.

General procedure 2: formation of Corey-Chaykovsky ylide

*n*BuLi (2.5 M, 1.0 equiv) was added dropwise to a solution of trimethylsufoxonium iodide (1.1 equiv) in anhydrous THF (0.75 M) at 0°C. The solution was allowed to warm to RT and stirring was continued under nitrogen for 1 hour. A solution 0.54 M of ylide was obtained.

General procedure 3: Cyclopropanation 1 (Corey-Chaykovsky)

A solution of ylide (1.1 equiv) in anhydrous THF (0.54 M) was added dropwise to a solution of the alkene derivative (1.0 equiv) in anhydrous THF (0.10 M) at RT under nitrogen. The mixture was stirred at the indicated temperature during the indicated time. The reaction was quenched with $NaHCO_3$ (10 mL/mmol) and extracted with Et_2O (3x10 mL/mmol). The combined organic layers were washed with brine (2x10 mL/mmol), dried over $MgSO_4$ and the solvent was removed under reduced pressure.

General procedure 4: formation of ketone from Weinreb's amide

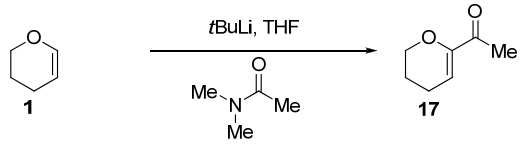
Following a slight modification of a reported procedure,[2] *t*BuLi (2.0 equiv) was added dropwise in a solution of alkene derivative (2.2 equiv) in THF (0.10 M) at -78°C. The flask was transferred in a bath of ice. After the indicated time the reaction was cooled to -78°C and a solution of amide (1.0 equiv) in THF (0.20 M) was added slowly dropwise. The reaction was stirred at -78°C during the indicated time and controlled via TLC. The solution was finally warmed at 0°C and quenched with saturate solution of NH_4Cl (5 mL/mmol). The product was extracted with Et_2O (10 mL/mmol of amide) and washed with brine (2x6 mL/mmol of amide), dried over $MgSO_4$ and concentrated under reduced pressure.

General procedure 5: cyclization

Toluenesulphonic acid (15 mg, 80 μmol, 0.20 equiv) was added to a solution of a vinyl cyclopropyl ketone derivative (0.40 mmol, 1.0 equiv) in anhydrous CH_3CN (10 mL) at room temperature. The reaction was stirred during the indicated time. The solution was quenched with $NaHCO_3$ (10 mL) and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure.

3 Substrates synthesis

2-Acetyl-5,6-dihydro-4*H*-pyran (17)

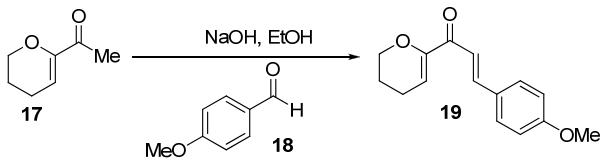


Following a reported procedure,[2] a 1.5 M solution of *t*BuLi in pentane (16 mL, 24 mmol 1.0 equiv) was added dropwise to a solution of 5,6-dihydro-4*H*-pyran (2.2 mL, 24 mmol, 1.0 equiv) in THF (15 mL) at -78°C. The reaction mixture was warmed to 0°C and stirred during 30 min then cooled to -78°C. A solution

[2] Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997-4006.

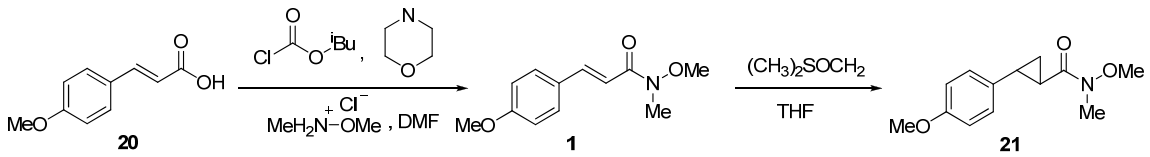
of dimethylacetamide (2.9 mL, 32 mmol, 1.3 equiv) in THF (2.0 mL) was added dropwise during 5 min and the reaction was allowed to warm slowly to RT. After 2 h the reaction was quenched with an aqueus saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (20x2 mL). The organic layers were combined and washed with sat NaCl, dried on $MgSO_4$ and evaporated under reduced pression. The crude product was purified by flash column chromatography (PET/AcOEt 3:1) to yield ketone **17** (2.4 g, 19 mmol, 80%) as yellow oil. R_f 0.60 (DCM/AcOEt 16:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.93 (t, *J* = 4.2 Hz, 1H; CH-alkene), 4.04 (t, *J* = 4.9 Hz, 2H; CH_2O), 2.21 (s, 3H; CH_3), 2.17 (app dd, *J* = 6.3, 10.7 Hz, 2H; CH_2 pyran), 1.80 (app dt, *J* = 6.1, 12.0 Hz, 2H; CH_2 pyran). ^{1}H NMR spectra corresponded to the literature values.[2]

(*E*)-2-[2-(4-Methoxyphenyl)-1-ethylenecarbonyl]-5,6-dihydro-4*H*-pyran (19)



Following a slight modification of the reported procedure,[3] NaOH (0.4 mL, 2.5 M) was added to a solution of **17** (0.50 g, 4.0 mmol, 1.0 equiv) in EtOH (8 mL) at RT. The reaction was stirred for 5 min then *p*-anisaldehyde **18** (0.50 mL, 4.0 mmol, 1.0 equiv) was added dropwise. The solution was quenched after 1 h and 30 min with water (10 mL) and extracted with Et_2O (20x2 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated and the crude product was purified by flash column chromatography (PET/AcOEt 4:1) to yield **19** (40 mg, 0.14 mmol, 50%) as yellow oil. R_f 0.70 (PET/AcOEt 4:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, *J* = 15.8 Hz, 1H; CH-Ar), 7.56 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.22 (d, *J* = 15.8 Hz, 1H; CHCO), 6.90 (d, *J* = 8.7 Hz, 2H; Ar-H), 6.09 (t, *J* = 4.2 Hz, 1H; alkene-H), 4.15 (t, *J* = 5.2 Hz, 2H; CH_2O), 3.84 (s, 3H; OCH_3), 2.26 (app dd, *J* = 6.3, 10.7 Hz, 2H; CH_2 pyran), 1.96 – 1.85 (m, 2H; CH_2 pyran). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.7, 161.2, 151.6, 143.3, 130.0, 127.3, 117.8, 114.0, 109.9, 66.0, 55.0, 21.3, 20.6. IR ν 2953 (w), 2934 (w), 2837 (w), 1660 (w), 1627 (m), 1589 (s), 1570 (s), 1510 (s), 1423 (m), 1327 (m), 1295 (m), 1281 (m), 1253 (s), 1235 (s), 1200 (m), 1171 (s), 1090 (m), 1059 (s), 1027 (s), 986 (m), 918 (s), 829 (s), 800 (m), 773 (m), 714 (m). HRMS(ESI) calcd for $C_{15}H_{16}O_3^+$ (M+H) 245.1172, found 245.1178.

(*E*)-*N*-Methoxy-*N*-methyl-3-(4-methoxyphenyl)-acrylamide (1) and *N*-methoxy-*N*-methyl-1-[2-(4-methoxyphenyl)-cyclopropan-1-yl]-formamide (21)

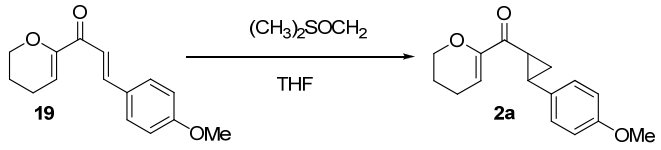


Following general procedure **1**, the acid **20** (2.00 g, 11.2 mmol, 1.00 equiv) gave the Weinreb amide **1** which was used directly without purification. Using general procedure **3**, a solution of ylide (12.2 mL, 6.58 mmol, 1.20 eq) was added to a solution of amide **1** (1.21 g, 5.47 mmol, 1.00 equiv) in THF (45 mL). The reaction was stirred at 40°C during 2 h then quenched. Purification by flash column chromatography (PET/AcOEt, 7:3) afforded **21** (824 mg, 3.50 mmol, 64 %) over 2 steps as oil. R_f 0.35 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.6 Hz, 2H; Ar-H), 6.83 (d, *J* = 8.7 Hz, 2H; Ar-H), 3.78 (s, 3H; OCH_3), 3.69 (s, 3H; OCH_3), 3.23 (s, 3H; NCH_3), 2.50 – 2.42 (m, 1H; cyclopropane CH),

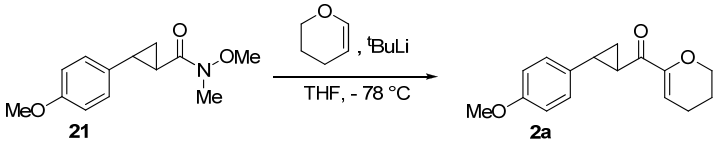
[3] Matsui, M.; Oji, A.; Hiramatsu, K.; Shibata, K.; Muramatsu, H. *J. Chem. Soc.-Perkin Trans. 2* **1992**, 201-206.

2.33 (m, 1H; cyclopropane CH), 1.65 – 1.55 (m, 1H; cyclopropane CH_2), 1.30 – 1.22 (m, 1H; cyclopropane CH_2). ^{1}H NMR spectra corresponded to the literature values.[1]

(*E*)-2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4*H*-pyran (2a)

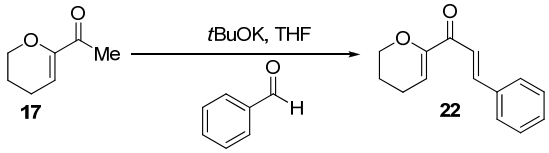


Following general procedure **3**, a solution of sulphoxonium ylide (2.90 mL, 1.57 mmol, 1.20 equiv) was added to a solution of alkene **19** (0.35 g, 1.4 mmol, 1.0 equiv) in THF (15 mL). The reaction was stirred at RT during 3 h and 30 min then quenched. Purification by flash column chromatography (PET/AcOEt 4:1) gave **2a** (0.2 g, 0.8 mmol, 55%) as yellow oil.



General procedure **4** was followed using dihydropyran (0.14 mL, 1.5 mmol, 2.2 equiv) and amide **21** (0.16 g, 0.68 mmol, 1.0 equiv). The deprotonation time was 30 min at 0°C and the reaction was quenched after 2 h and 15 min to give **2a** (105 mg, 410 µmol, 60%) after purification via flash chromatography (PET/AcOEt, 7:3) as yellow oil. R_f 0.70 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.6 Hz, 2H; Ar H), 6.83 (d, *J* = 8.7 Hz, 2H; Ar-H), 6.01 (t, *J* = 4.2 Hz, 1H; alkene-H), 4.14 – 4.06 (m, 2H; CH_2O), 3.79 (s, 3H; OCH_3), 2.71 – 2.59 (m, 1H; CH cyclopropane), 2.54 (ddd, *J* = 4.1, 6.6, 10.5 Hz, 1H; CH cyclopropane), 2.22 (dd, *J* = 6.3, 10.7 Hz, 2H; CH_2 dihydropyran), 1.92 – 1.81 (m, 2H; CH_2 dihydropyran), 1.76 – 1.67 (m, 1H; CH_2 cyclopropane), 1.37 (ddd, *J* = 4.0, 6.8, 8.0 Hz, 1H; CH_2 cyclopropane). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.6, 158.2, 151.4, 132.5, 127.2, 113.8, 109.5, 66.3, 55.2, 29.3, 27.30, 21.4, 20.7, 19.2. IR ν 3036 (w), 2950 (w), 2934 (w), 2836 (w), 1681 (m), 1667 (m), 1625 (s), 1516 (s), 1440 (m), 1393 (m), 1331 (m), 1286 (s), 1248 (s), 1237 (m), 1201 (w), 1180 (s), 1091 (m), 1061 (s), 1032 (s), 999 (m), 917 (s), 822 (s), 751 (s). HRMS(ESI) calcd for $C_{16}H_{18}O_3^+$ (M+H) 259.1329, found 259.1335.

(*E*)-2-[2-(Phenyl)-1-ethylenecarbonyl]-5,6-dihydro-4*H*-pyran (22)

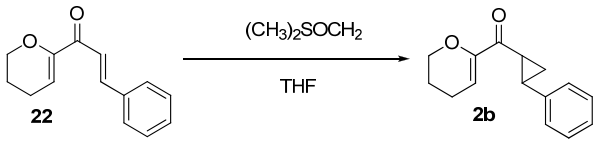


Following a slight modification of the reported procedure[4] *t*BuOK (44 mg, 0.40 mmol, 0.10 equiv) was added to a solution of **17** (0.50 g, 4.0 mmol, 1.0 equiv) in THF (40 mL) at 0°C. The reaction was stirred at 0°C for 5 min then benzaldehyde (0.60 mL, 6.0 mmol, 1.5 equiv) was added dropwise. The solution was quenched after 30 min with water (10 mL) and extracted with Et_2O (2x20 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated and separated by flash column chromatography (PET/AcOEt 4:1) to yield **22** (39 mg, 0.14 mmol, 40%) as yellow oil. R_f 0.40 (PET/AcOEt 6:1,

[4] Ishikawa, T.; Aikawa, T.; Ohata, E.; Iseki, T.; Maeda, S.; Matsuo, T.; Fujino, T.; Saito, S. *J. Org. Chem.* **2007**, *72*, 435-441.

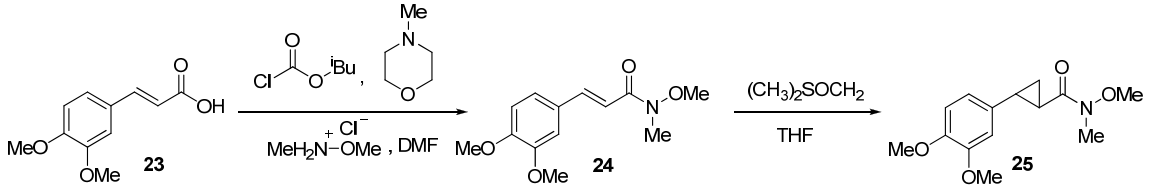
Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, *J* = 15.8 Hz, 1H; alkene-H), 7.60 (dd, *J* = 2.9, 6.6 Hz, 2H; Ph-H), 7.41 – 7.37 (m, 3H; Ph-H), 7.33 (d, *J* = 15.8 Hz, 1H; alkene-H), 6.12 (t, *J* = 4.3 Hz, 1H; alkene-H), 4.25 – 4.08 (m, 2H; CH_2O), 2.27 (dd, *J* = 6.3, 10.7 Hz, 2H; CH_2 pyran), 1.98 – 1.82 (m, 2H; CH_2 pyran). ^{1}H NMR spectra corresponded to the literature values.[5]

2-[2-(Phenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4*H*-pyran (2b)



Following general procedure **3**, a solution of sulphoxonium ylide (1.1 mL, 0.58 mmol, 1.2 equiv) was added to a solution of alkene **22** (0.104 mg, 0.485 mmol, 1.00 equiv) in THF (5 mL). The reaction was stirred at RT during 15 min then quenched. Purification by flash column chromatography (PET/AcOEt 4:1) gave **2b** (204 mg, 0.790 mmol, 50%) as colorless oil. R_f 0.80 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (dd, *J* = 4.7, 12.4 Hz, 2H; Ph-H), 7.20 (t, *J* = 7.3 Hz, 1H; Ph-H), 7.12 (d, *J* = 7.2 Hz, 2H; Ph-H), 6.02 (t, *J* = 4.2 Hz, 1H; H-alkene), 4.16 – 4.04 (m, 2H; CH_2O), 2.80 – 2.67 (m, 1H; CH cyclopropane), 2.62 – 2.51 (m, 1H; CH cyclopropane), 2.22 (dd, *J* = 6.3, 10.7 Hz, 2H; CH_2 dihydropyran), 1.93 – 1.80 (m, 2H; CH_2 dihydropyran), 1.75 (ddd, *J* = 4.1, 5.2, 9.2 Hz, 1H; CH_2 cyclopropane), 1.42 (ddd, *J* = 4.0, 6.6, 8.1 Hz, 1H; CH_2 cyclopropane). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 151.3, 140.4, 128.3, 126.3, 126.1, 109.7, 66.3, 29.7, 27.3, 21.44, 20.7, 19.6. IR ν 2958 (s), 2928 (s), 1737 (w), 1666 (m), 1627 (s), 1510 (m), 1497 (m), 1458 (m), 1398 (m), 1341 (m), 1287 (s), 1261 (m), 1237 (m), 1205 (m), 1182 (s), 1159 (m), 1081 (s), 1061 (s), 1030 (s), 1007 (s), 919 (s), 795 (s), 756 (s), 699 (s). HRMS(ESI) calcd for $C_{15}H_{16}O_2^+$ (M+H) 251.1042, found 251.1037.

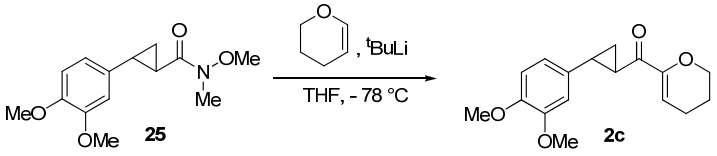
(*E*)-*N*-Methoxy-*N*-methyl-3-(3,4-dimethoxyphenyl)-acrylamide (24) and *N*-methoxy-*N*-methyl-1-[2-(3,4-dimethoxyphenyl)-cyclopropan-1-yl]-formamide (25)



Following general procedure **1**, the acid **23** (1.74 g, 8.36 mmol, 1.00 equiv) gave the Weinreb amide **24** which was used directly without purification. Using general procedure **3**, a solution of ylide (16.5 mL, 8.91 mmol, 1.20 eq) was added to a solution of amide **24** (1.85 g, 7.36 mmol, 1.00 equiv) in THF (75 mL). The reaction was stirred at room temperature during 3 h then quenched. Purification by flash column chromatography (PET/ AcOEt, 3/2) afforded **25** (918 mg, 3.45 mmol, 47%) over 2 steps as colorless oil. R_f 0.30 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79 (d, *J* = 8.2 Hz, 1H; Ar-H), 6.73 – 6.64 (m, 2H; Ar-H), 3.87 (s, 3H; OCH_3), 3.85 (s, 3H; OCH_3), 3.70 (s, 3H; OCH_3), 3.24 (s, 3H; NCH_3), 2.55 – 2.41 (m, 1H; CH cyclopropane), 2.33 (s, 1H; CH cyclopropane), 1.59 (dt, *J* = 4.8, 9.3 Hz, 1H; CH_2 cyclopropane), 1.27 (ddd, *J* = 5.7, 8.8, 17.5 Hz, 1H; CH_2 cyclopropane). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.0, 148.8, 147.5, 133.2, 117.9, 111.2, 110.2, 61.6, 55.8, 55.7, 32.4, 25.6, 21.3, 15.9. IR ν 3006 (w), 2963 (w), 2938 (w), 2837 (w), 1645 (w), 1518 (m), 1464 (m), 1441 (w), 1420 (w), 1392 (w), 1254 (m), 1235 (m), 1141 (m), 1028 (m), 1004 (w), 907 (s), 805 (w), 726 (s), 648 (m). HRMS(ESI) calcd for $C_{14}H_{19}NO_4^+$ (M+H) 266.1387, found 266.1385.

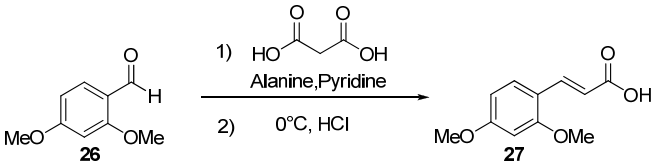
[5] Liang, G. X.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931-4934.

2-[2-(3,4-Methoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4*H*-pyran (2c)



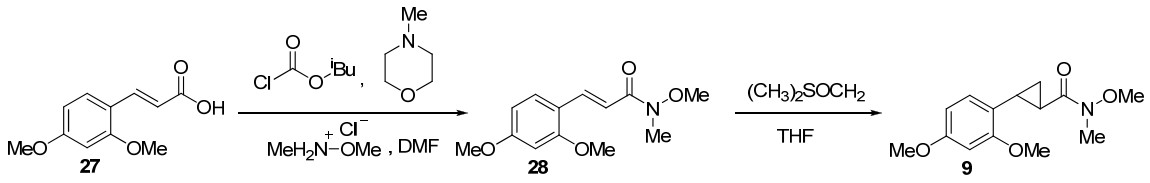
Following general procedure **4**, dihydropyran (344 µL, 3.77 mmol, 2.20 equiv) and amide **25** (450 mg, 1.71 mmol, 1.00 equiv) were reacted together. The deprotonation time was 45 min at 0°C and the reaction was quenched after 45 min. Purification by flash chromatography (PET/AcOEt, 7:3) afforded **2c** (158 mg, 0.550 mmol, 32 %) as colorless oil. R_f 0.40 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.79 (d, *J* = 8.8 Hz, 1H; Ar-H), 6.67 (d, *J* = 6.2 Hz, 2H; Ar-H), 6.02 (t, *J* = 4.2 Hz, 1H; alkene-H), 4.17 – 4.07 (m, 2H; CH_2O), 3.87 (s, 3H; OCH_3), 3.85 (s, 3H; OCH_3), 2.70 – 2.61 (m, 1H; cyclopropane CH), 2.54 (ddd, *J* = 4.1, 6.7, 10.6 Hz, 1H; cyclopropane CH), 2.22 (dd, *J* = 6.3, 10.7 Hz, 2H; dihydropyran CH_2), 1.92 – 1.81 (m, 2H; dihydropyran CH_2), 1.71 (ddd, *J* = 4.2, 5.1, 9.1 Hz, 1H; cyclopropane CH_2), 1.39 (ddd, *J* = 4.0, 6.7, 8.1 Hz, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.7, 151.4, 148.8, 147.7, 133.1, 117.9, 111.2, 110.0, 109.6, 66.3, 55.9, 55.8, 29.6, 27.5, 21.5, 20.7, 19.2. IR ν 3002 (w), 2935 (w), 2836 (w), 2252 (w), 1663 (w), 1625 (m), 1590 (w), 1518 (s), 1464 (m), 1439 (w), 1389 (m), 1287 (m), 1255 (m), 1235 (s), 1203 (m), 1181 (m), 1141 (m), 1091 (m), 1062 (m), 1027 (s), 962 (w), 913 (s), 806 (m), 729 (s). HRMS(ESI) calcd for $C_{17}H_{20}O_4^+$ (M+H) 289.1424, found 289.1434.

(*E*)-2,4-Dimetoxy-*cis*-cinnamic acid (27)



Following a reported procedure,[6] a solution of aldehyde **27** (11.0 g, 66.7 mmol, 1.00 equiv), malonic acid (17.5 g, 168 mmol, 2.50 equiv) and β-alanine (1.0 g, 89 mmol, 0.20 equiv) in pyridine (3 mL) was stirred under reflux for 90 min. After cooling to RT, the flask was transferred in an ice bath and a concentrated solution of HCl (8 mL) was added dropwise. The precipitate was filtered, washed with cold water (2x10mL) and dried without further purification to give **27** as light yellow solid (12.5 g, 60.0 mmol, 90%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.11 (s, 1H; OH), 7.75 (d, *J* = 16.1 Hz, 1H; CH-Ar), 7.61 (d, *J* = 8.6 Hz, 1H; Ar-H), 6.64 – 6.54 (m, 2H; Ar-H), 6.37 (d, *J* = 16.1 Hz, 1H; CHCO), 3.86 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3). ^{1}H NMR spectra corresponded to the literature values.[7]

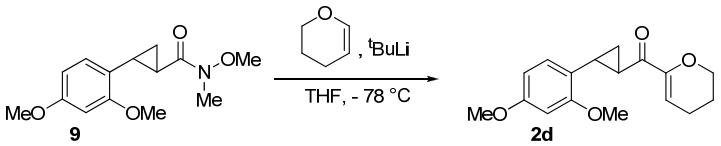
(*E*)-*N*-Methoxy-*N*-methyl-3-(2,4-dimethoxyphenyl)-acrylamide (28) and *N*-methoxy-*N*-methyl-1-[2-(2,4-dimethoxyphenyl)-cyclopropan-1-yl]-formamide (9)



[6] Stabile, R. G.; Dicks, A. R. *J. Chem. Educ.* **2004**, *81*, 1488-1491.
[7] Luadthong, C.; Tachaprutinun, A.; Wanichwecharungruang, S. P. *Eur. Polym. J.* **2008**, *44*, 1285-1295.

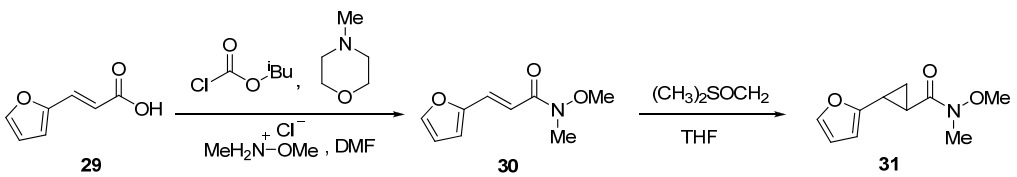
Following general procedure **1**, the acid **27** (12.47 g, 59.89 mmol, 1.000 equiv) gave the Weinreb amide **28** which was used directly without purification. Using general procedure **3**, a solution of ylide (53.4 mL, 28.8 mmol, 1.20 eq) was added to a solution of amide **28** (6.00 g, 23.9 mmol, 1.00 equiv) in THF (240 mL). The reaction was stirred at RT overnight then quenched. Purification by flash column chromatography (PET/AcOEt, 3:2) gave 9 (3.93 g, 14.8 mmol, 62%) over 2 steps as white solid. R_f 0.35 (PET/AcOEt 3:2, Anisaldehyde). Mp 58 -59 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (d, J = 8.3 Hz, 1H; Ar-H), 6.46 – 6.37 (m, 2H; Ar-H), 3.80 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.24 (s, 3H; NCH_3), 2.64 – 2.51 (m, 1H; CH cyclopropane), 2.25 (s, 1H; CH cyclopropane), 1.57 – 1.49 (m, 1H; CH_2 cyclopropane), 1.30 – 1.20 (m, 1H; CH_2 cyclopropane). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 159.4, 159.2, 126.6, 121.2, 103.7, 98.3, 61.3, 55.2, 55.2, 32.5, 20.7, 19.8, 14.3. IR ν 3002 (w), 2960 (w), 2938 (w), 2837 (w), 1650 (s), 1614 (m), 1585 (m), 1510 (s), 1461 (s), 1438 (s), 1417 (s), 1394 (m), 1364 (m), 1321 (w), 1289 (s), 1263 (m), 1208 (s), 1176 (s), 1159 (s), 1155 (s), 1127 (s), 1096 (m), 1033 (s), 933 (m), 920 (m), 874 (w), 834 (s), 800 (w), 775 (w), 729 (w). HRMS(ESI) calcd for $C_{14}H_{19}NO_4^+$ (M+H) 266.1387, found 266.1381.

2-[2-(2,4-Dimethoxyphenyl)-1-cyclopropanecarbonyl]-5,6-dihydro-4*H*-pyran (2d)



Following general procedure **4**, a solution of amide **9** (400 mg, 1.51 mmol, 1.00 equiv) was added to a solution of dihydropyran (345 µL, 3.77 mmol, 2.50 equiv). The deprotonation time was 30 min at 0°C and the reaction was quenched after 2 h and 15 mins to give **2d** (305 mg, 1.01 mmol, 70%) as yellow oil after purification via flash chromatography (PET/AcOEt, 7:3). R_f 0.55 (PET/ AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, J = 8.2 Hz, 1H; Ar-H), 6.41 (dd, J = 2.3, 10.6 Hz, 2H; Ar-H), 6.02 (t, J = 4.2 Hz, 1H; alkene-H), 4.13 – 4.08 (m, 2H; CH_2O), 3.79 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 2.74 – 2.62 (m, 1H; cyclopropane CH), 2.57 (dt, J = 4.8, 9.3 Hz, 1H; cyclopropane CH), 2.22 (dd, J = 6.3, 10.7 Hz, 2H; dihydropyran CH_2), 1.92 – 1.81 (m, 2H; dihydropyran CH_2), 1.71 – 1.63 (m, 1H; cyclopropane CH_2), 1.36 (td, J = 3.8, 7.6 Hz, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.2, 159.4, 159.2, 151.5, 126.5, 121.4, 109.4, 103.8, 98.3, 66.23, 55.3, 25.9, 24.7, 21.5, 20.7, 17.8. IR ν 3010 (w), 2957 (w), 2936 (w), 2837 (w), 1681 (m), 1666 (m), 1625 (s), 1586 (m), 1510 (m), 1464 (m), 1436 (m), 1397 (m), 1333 (m), 1289 (s), 1265 (w), 1237 (w), 1209 (s), 1182 (m), 1160 (m), 1124 (w), 1092 (w), 1063 (s), 1034 (s), 1002 (w), 954 (w), 918 (m), 837 (w). HRMS(ESI) calcd for $C_{17}H_{20}O_4^+$ (M+H) 289.1434, found 289.1412.

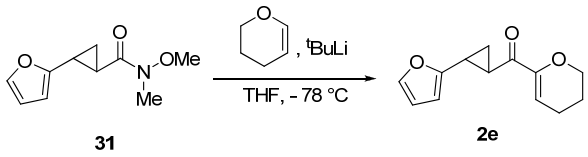
(*E*)-*N*-Methoxy-*N*-methyl-3-(2-furanyl)-acrylamide (30) and *N*-methoxy-*N*-methyl-1-[2-(2-furanyl)-cyclopropan-1-yl]-formamide (31)



Following general procedure **1**, the acid **29** (1.55 g, 11.2 mmol, 1.00 equiv) gave the Weinreb amide **30** which was used directly without purification. Using the general procedure **3**, a solution of ylide (10 mL, 5.4 mmol, 1.2 eq) was added to a solution of amide **31** (810 g, 4.47 mmol, 1.00 equiv) in THF (46 mL). The reaction was warmed to 40°C and stirred during 3 h before quenching. Purification by flash column chromatography (PET/AcOEt, 7:3) gave **28** (436 mg, 2.24 mmol, 50%) over two steps as colorless oil. R_f 0.50 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 – 7.25 (m, 1H; furan-H), 6.28

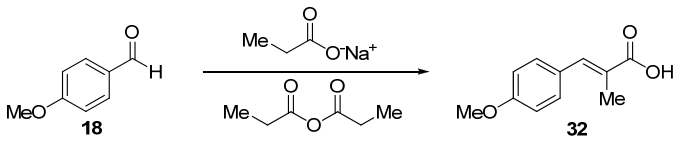
(dd, *J* = 1.9, 3.0 Hz, 1H; furan-H), 6.07 (d, *J* = 3.1 Hz, 1H; furan-H), 3.73 (s, 3H; OCH_3), 3.23 (s, 3H; NCH_3), 2.58 – 2.40 (m, 2H; 2xCH cyclopropane), 1.59 – 1.50 (m, 1H; CH_2 cyclopropane), 1.44 – 1.32 (m, 1H; CH_2 cyclopropane). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 153.7, 140.8, 110.3, 105.0, 61.5, 32.4, 19.2, 18.9, 14.0. IR ν 3522 (w), 2938 (w), 1648 (s), 1509 (m), 1462 (m), 1440 (s), 1423 (s), 1389 (m), 1354 (m), 1176 (m), 1148 (m), 1115 (m), 1098 (m), 995 (s), 952 (m), 914 (m), 801 (m), 733 (s). HRMS(ESI) calcd for $C_{10}H_{13}NO_3^+$ (M+H) 196.0968, found 196.0975.

2-[2-(Furan-2-yl)-1-cyclopropanecarbonyl]-5,6-dihydro-4*H*-pyran (2e)



Following general procedure **4**, dihydropyran (400 μL, 4.40 mmol, 2.00 equiv) and amide **31** (430 mg, 2.20 mmol, 1.00 equiv) were reacted together. The deprotonation time was 30 min at 0°C and the reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 9:1) afforded **2e** (300 mg, 1.38 mmol, 63 %) as a yellow oil. R_f 0.25 (PET/AcOEt 10:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.26 (m, 1H; Ar-H), 6.29 (s, 1H; Ar-H), 6.08 (s, 1H; Ar-H), 6.04 (t, *J*= 3.9 Hz, 1H; alkene-H), 4.16 – 4.07 (m, 2H; CH_2O), 2.89 – 2.73 (m, 1H; cyclopropane CH), 2.57 (t, *J*= 9.6 Hz, 1H; cyclopropane CH), 2.23 (dd, *J*= 5.8, 10.6 Hz, 2H; dihydropyran CH_2), 1.87 (dd, *J*= 5.6, 10.8 Hz, 2H; dihydropyran CH_2), 1.67 – 1.58 (m, 1H; cyclopropane CH_2), 1.47 (t, *J*= 9.0 Hz, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.6, 153.4, 150.9, 140.6, 110.1, 109.7, 104.9, 65.9, 24.6, 22.1, 21.1, 20.4, 16.8. IR ν 3118 (w), 2932 (w), 2873 (w), 1683 (m), 1668 (m), 1626 (s), 1509 (w), 1445 (w), 1431 (w), 1385 (m), 1350 (w), 1314 (w), 1287 (m), 1246 (m), 1236 (m), 1202 (m), 1180 (m), 1149 (w), 1091 (m), 1061 (s), 1034 (m), 1008 (m), 991 (m), 955 (w), 916 (s), 886 (w), 797 (m), 789 (m), 730 (s). HRMS(ESI) calcd for $C_{13}H_{14}O_3^+$ (M+H) 219.1016, found 219.1011.

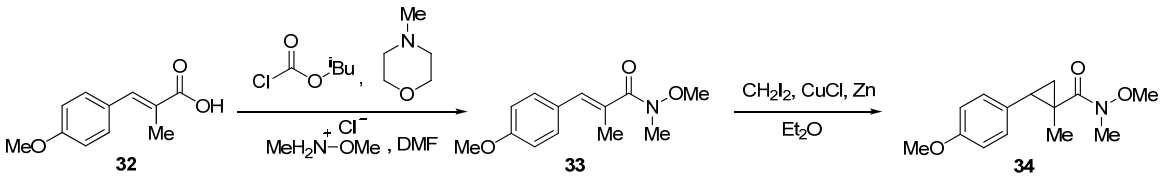
(*E*)-3-(4-Methoxyphenyl)-2-methyl-acrylic acid (32)



Following a reported procedure,[8] a mixture of anisaldehyde **18** (10 mL, 82 mmol, 1.0 equiv), propionic anhydride (19 mL, 0.16 mol, 2.0 equiv) and sodium propionate (7.9 g, 82 mmol, 1.0 equiv) was heated at 150 °C for 12 h. After cooling to 23 °C, 4 M NaOH solution (60 mL) was added and the mixture was washed with Et_2O (2x20 mL). The water layer was acidified to pH = 1 with conc. HCl and the precipitated colorless solid was washed with water and dried in high vacuo to give **32** as a colorless solid (10.0 g, 52.1 mmol, 63%). Mp 154-157 °C, Lit [8]: 152-155 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (br s, 1H; alkene-H), 7.43 (d, *J* = 8.6 Hz, 2H; Ar-H), 6.95 (d, *J* = 9.0 Hz, 2H; Ar-H), 3.85 (s, 3H; OCH_3), 2.16 (d, *J* = 1.6 Hz, 3H; $CHCH_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 160.0, 140.8, 131.7, 128.2, 125.2, 113.9, 55.3, 13.7. IR ν 2939 (w), 2838 (w), 2634 (w), 2512 (w), 1661 (m), 1600 (m), 1569 (m), 1511 (m), 1424 (m), 1320 (m), 1275 (s), 1253 (s), 1180 (m), 1130 (m), 1030 (m), 912 (s), 829 (s), 808 (s), 746 (s), 693 (m), 652 (w). ^{1}H NMR and IR spectra corresponded to the literature values.[8]

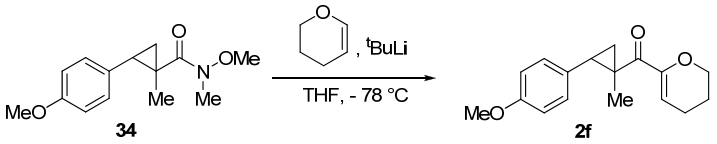
[8] Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636-3658.

(*E*)-*N*-Methoxy-*N*-methyl-3-(4-methoxyphenyl)-2-methyl-acrylamide (33) and *N*-methoxy-*N*-methyl-1-[2-(4-methoxyphenyl)-cyclopropan-1-methyl-1-yl]-formamide (34)



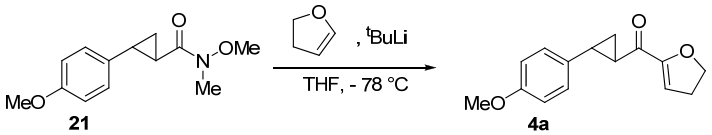
Following general procedure **1**, the acid **32** (3.00 g, 15.6 mmol, 1.00 equiv) gave the Weinreb amide **33** which was used directly without purification. A suspension of copper(I) chloride (1.5 g, 15 mmol, 5.0 equiv, purified via precipitation from a solution in conc. HCl, washed with water, EtOH, Et_2O and dried in HV) and Zinc dust (activated with 1% HCl, washed with water, EtOH, Et_2O and dried in HV, 1.0 g, 15 mmol, 5.0 equiv) in Et_2O (7 mL) was refluxed for 30 min. The reaction mixture was cooled to 23 °C and a solution of Weinreb amide **33** (0.71 g, 3.0 mmol, 1.0 equiv) in Et_2O (2 mL) was added. After refluxing for 72 h, the reaction mixture was cooled to 23 °C and quenched with sat. NH_4Cl (5 mL). Water (5 mL) was added and the reaction mixture was extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5:1-4:1) to yield cyclopropane **34** (0.15 g, 0.61 mmol, 20%, 61% brsm) as a colorless oil as well as recovered starting material **33** (0.47 g, 2.0 mmol, 66%). R_f 0.55 (PET/AcOEt 1:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (dd, *J* = 9.0, 0.6 Hz, 2H; Ar-H), 6.85 (d, *J* = 8.6 Hz, 2H; Ar-H), 3.80 (s, 3H; OCH_3), 3.76 (s, 3H; OCH_3), 3.25 (s, 3H, NCH_3), 2.44 (dd, *J* = 9.3, 6.7 Hz, 1H; cyclopropane CH), 1.59 (m, 1 H, cyclopropane CH_2), 1.06 (s, 3 H, cyclopropane-CH_3), 0.96 (dd, *J* = 6.7, 5.1 Hz, 1 H, cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 158.1, 130.0, 129.3, 113.5, 60.8, 55.1, 33.8, 27.1, 26.7, 17.1, 16.1. IR ν 2934 (w), 1646 (m), 1515 (s), 1463 (m), 1247 (s), 1176 (m), 1029 (m), 911 (s), 837 (m), 730 (s), 647 (w). HRMS(ESI) calcd for $C_{14}H_{19}NO_3^+$ (M+Na) 272.1257, found 272.1259.

2-[2-(4-Methoxyphenyl)-1-methyl-1-cyclopropanecarbony]-5,6-dihydro-4*H*-pyran (2f)



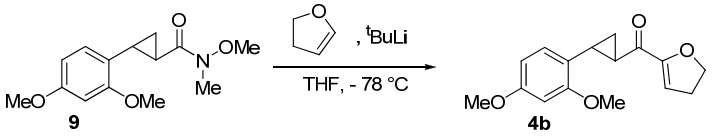
Following general procedure **4**, dihydropyran (44 mL, 0.48 mmol, 2.0 equiv) and amide **34** (59 mg, 0.24 mmol, 1.0 equiv) were reacted together. The deprotonation time was 30 min at 0°C and the reaction was quenched after 30 min. Purification by flash chromatography (PET/AcOEt 10:1-5:1) afforded **2f** (39 mg, 0.14 mmol, 60%) as colorless oil. R_f 0.70 (PET/ AcOEt 2:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (d, *J* = 8.0 Hz, 2H; Ar-H), 6.85 (d, *J* = 8.6 Hz, 2H; Ar-H), 5.80 (t, *J* = 4.2 Hz, 1H; alkene-H), 4.09 (m, 2H; CH_2O), 3.79 (s, 3H; OCH_3), 2.50 (dd, *J* = 9.0, 6.7 Hz, 1H; cyclopropane CH), 2.20 (m, 2H; dihydropyran CH_2), 1.87 (m, 2H; dihydropyran CH_2), 1.82 (dd, *J* = 9.3, 4.8 Hz, 1H; cyclopropane CH_2), 1.07 (s, 3H; cyclopropane-CH_3), 1.02 (dd, *J* = 6.7, 4.8 Hz, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.3, 158.2, 151.5, 130.1, 129.1, 113.5, 109.2, 65.9, 55.2, 31.8, 30.4, 21.6, 20.5, 18.2, 15.9. IR ν 2956 (w), 2930 (w), 1669 (w), 1624 (m), 1613 (m), 1515 (s), 1463 (w), 1444 (w), 1382 (w), 1290 (m), 1247 (s), 1173 (m), 1061 (m), 1036 (m), 1003 (m), 916 (s), 836 (m), 732 (s), 648 (w). HRMS(ESI) calcd for $C_{17}H_{20}O_3^+$ (M-H) 271.1329, found 271.1333.

2-[2-(4-Methoxy-phenyl)-1-cyclopropanecarbonyl]-4,5-dihydro-furan (4a)



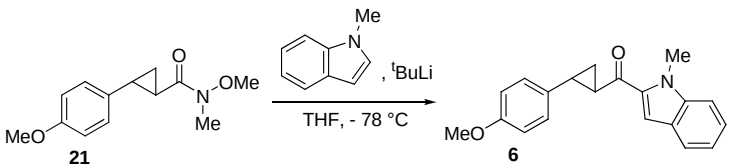
The reaction was carried out following general procedure **4** from dihydrofuran (353 µL, 4.67 mmol, 2.20 equiv) and amide **21** (500 mg, 2.12 mmol, 1.00 equiv). The deprotonation time was 30 min at 0°C and the reaction was quenched after 1 hour. Purification by flash chromatography (PET/AcOEt, 7:3) afforded **4a** (517 mg, 2.12 mmol, 100%) as colorless oil. R_f 0.55 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (d, *J* = 8.7 Hz, 2H; Ar-H), 6.83 (d, *J* = 8.6 Hz, 2H; Ar-H), 5.99 (t, *J* = 3.1 Hz, 1H; alkene-H), 4.49 (t, *J* = 9.8 Hz, 2H; CH_2O), 3.79 (s, 3H; OCH_3), 2.84 (td, *J* = 3.1, 9.8 Hz, 2H; dihydrofuran CH_2), 2.63 – 2.54 (m, 1H; cyclopropane CH), 2.52 – 2.44 (m, 1H; cyclopropane CH), 1.79 – 1.72 (m, 1H; cyclopropane CH_2), 1.44 – 1.37 (m, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 158.4, 155.8, 132.2, 127.3, 113.9, 111.3, 70.3, 55.3, 30.7, 29.4, 29.4, 19.0. IR ν 3004 (w), 2936 (w), 2836 (w), 1649 (s), 1614 (m), 1516 (s), 1462 (m), 1442 (m), 1421 (m), 1394 (w), 1367 (w), 1303 (w), 1289 (w), 1248 (s), 1177 (m), 1122 (m), 1097 (m), 1035 (m), 997 (m), 942 (w), 824 (m), 809 (m), 767 (w), 743 (w). HRMS(ESI) calcd for $C_{15}H_{16}O_5^+$ (M+H) 245.1172, found 245.1178.

2-[2-(2,4-Methoxy-phenyl)-1-cyclopropanecarbonyl]-4,5-dihydro-furan (4b)



Amide **9** (400 mg, 1.51 mmol, 1.00 equiv) was added to dihydrofuran (285 µL, 3.77 mmol, 2.50 equiv), following general procedure **4**. The deprotonation time was 30 min at 0°C and the reaction was quenched after 45 min to give **4b** (414 mg, 1.51 mmol, 100%) as white solid without further purification. R_f 0.45 (PET/AcOEt 7:3, Anisaldehyde). Mp 100-102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (d, *J* = 8.2 Hz, 1H; Ar-H), 6.41 (dt, *J* = 2.3, 8.3 Hz, 2H; Ar-H), 5.98 (t, *J* = 3.1 Hz, 1H; alkene-H), 4.57 – 4.41 (m, 2H; CH_2O), 3.79 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 2.84 (td, *J* = 3.1, 9.8 Hz, 2H; dihydrofuran CH_2), 2.70 (ddd, *J* = 4.2, 7.1, 9.0 Hz, 1H; cyclopropane CH), 2.41 (dt, *J* = 4.9, 8.1 Hz, 1H; cyclopropane CH), 1.79 – 1.65 (m, 1H; cyclopropane CH_2), 1.41 (td, *J* = 3.9, 7.6 Hz, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.2, 159.6, 159.3, 156.0, 126.7, 121.0, 111.0, 103.8, 98.4, 70.2, 55.3, 30.7, 28.0, 25.0, 17.5. IR ν 3103 (w), 3000 (w), 2959 (w), 2936 (w), 2836 (w), 1663 (m), 1613 (s), 1585 (m), 1509 (m), 1466 (m), 1456 (m), 1436 (m), 1410 (m), 1342 (w), 1291 (m), 1264 (m), 1209 (s), 1175 (m), 1160 (m), 1060 (m), 1044 (s), 1013 (m), 940 (m), 905 (w), 838 (m), 799 (w), 729 (w). HRMS(ESI) calcd for $C_{16}H_{18}O_4^+$ (M+H) 275.1278, found 275.1240.

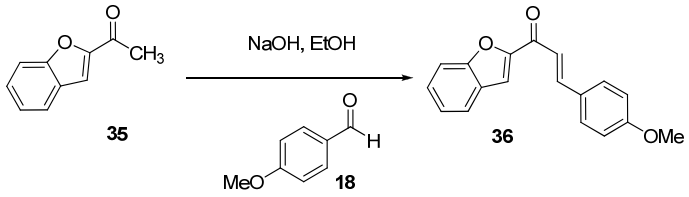
2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-1-methylindole (6)



Following general procedure **4**, *N*-methylindole (192 µL, 1.50 mmol, 2.20 equiv) was added to amide **21** (160 mg, 0.680 mmol, 1.00 equiv). The deprotonation time was 15 min at 0°C and the reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 7:3) afforded **8** (105 mg, 0.340

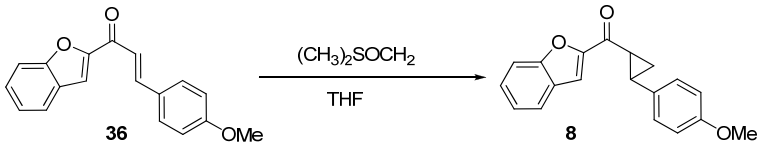
mmol, 50%) as white crystals. R_f 0.80 (PET/AcOEt 7:3, Anisaldehyde). Mp 103-105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, *J* = 8.0 Hz, 1H; Ar-H), 7.41 – 7.35 (m, 3H; Ar-H), 7.19 – 7.09 (m, 3H; Ar-H), 6.86 (d, *J* = 8.7 Hz, 2H; Ar-H), 4.10 (s, 3H; NCH_3), 3.81 (s, 3H; OCH_3), 2.91 – 2.78 (m, 1H; cyclopropane CH), 2.65 (ddd, *J* = 4.1, 6.7, 10.4 Hz, 1H; cyclopropane CH), 1.91 – 1.80 (m, 1H; cyclopropane CH_2), 1.47 (ddd, *J* = 4.2, 6.7, 8.0 Hz, 1H; cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 158.4, 140.1, 135.6, 132.6, 127.5, 125.9, 122.8, 120.6, 114.0, 111.5, 110.3, 55.3, 32.2, 30.6, 28.7, 18.2. IR ν 3002 (w), 2961 (w), 2937 (w), 2835 (w), 1648 (s), 1614 (m), 1515 (s), 1466 (m), 1439 (w), 1428 (w), 1404 (m), 1380 (w), 1323 (w), 1293 (w), 1250 (s), 1195 (m), 1163 (w), 1152 (w), 1129 (w), 1032 (m), 991 (m), 913 (w), 824 (w), 748 (m). HRMS(ESI) calcd for $C_{20}H_{19}NO_2^+$ (M+H) 306.1489, found 306.1475.

(*E*)-2-[2-(4-Methoxyphenyl)-1-ethylenecarbonyl]-benzofurane (36)



Following a slight modification of the reported procedure,[3] NaOH (4.4 mL, 2.5 M) was added to a solution of **35** (2.50 g, 15.6 mmol, 1.00 equiv) in EtOH (40 mL) at RT. The reaction was stirred for 5 min then *p*-anisaldehyde **18** (1.90 mL, 15.6 mmol, 1.00 equiv) was added dropwise. The solution was quenched after 30 min with water (20 mL) and extracted with Et_2O (40x2 mL). The organic layer was washed with brine, dried over $MgSO_4$, concentrated and purified by flash column chromatography (PET/AcOEt 9:1) to yield **36** (1.74 g, 6.25 mmol, 40%) as yellow oil. R_f 0.70 (PET/AcOEt 7:3, Anisaldehyde). Mp 125-127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, *J* = 15.7, 1H; CH-Ar), 7.73 (d, *J* = 7.8 Hz, 1H; Ar-H), 7.66 (d, *J* = 8.7 Hz, 2H; Ar-H), 7.63 (d, *J* = 6.7 Hz, 2H; Ar-H), 7.45 (m, 1H; Ar-H), 7.45 (d, *J* = 15.7 Hz, 1H; CHCO), 7.33 (t, *J* = 7.5 Hz, 1H; Ar-H), 6.96 (d, *J* = 8.7 Hz, 2H; Ar-H), 3.87 (s, 3H; OCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.6, 161.9, 155.6, 153.8, 144.4, 130.5, 128.0, 127.3, 123.8, 123.1, 118.7, 114.4, 112.7, 112.3, 55.3. IR ν 3137 (w), 3065 (w), 2844 (w), 1652 (s), 1589 (s), 1571 (s), 1557 (s), 1510 (s), 1475 (m), 1447 (m), 1424 (s), 1361 (w), 1348 (m), 1295 (s), 1262 (s), 1248 (s), 1194 (m), 1177 (s), 1160 (s), 1139 (s), 1036 (s), 1024 (s), 983 (s), 934 (s), 910 (s), 880 (s), 855 (m), 819 (s), 784 (s), 735 (s). HRMS(ESI) calcd for $C_{18}H_{14}O_3^+$ (M+H) 279.1016, found 279.0999.

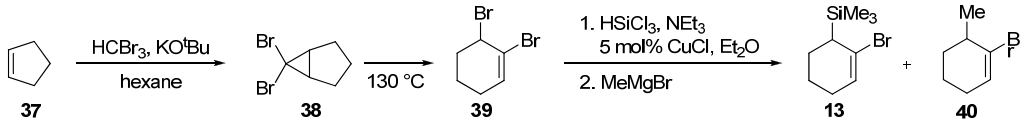
2-[2-(4-Methoxyphenyl)-1-cyclopropanecarbonyl]-benzofurane (8)



Following general procedure **3**, a solution of sulphoxonium ylide (5.9 mL) was added to a solution of alkene **36** (800 mg, 2.90 mmol, 1.00 equiv) in THF (30 mL). The reaction was stirred at RT during 45 min then quenched. Purification by flash column chromatography (PET/AcOEt 4:1) gave **8** (384 mg, 1.31 mmol, 45%) as white crystals. R_f 0.80 (PET/AcOEt 7:3, Anisaldehyde). Mp 115-117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 7.9 Hz, 1H; Ar-H), 7.61 – 7.52 (m, 2H; Ar-H), 7.47 (dd, *J* = 4.1, 11.4 Hz, 1H; Ar-H), 7.31 (t, *J* = 7.5 Hz, 1H; Ar-H), 7.13 (d, *J* = 8.6 Hz, 2H; Ar-H), 6.87 (d, *J* = 8.7 Hz, 2H; Ar-H), 3.81 (s, 3H; OCH_3), 3.00 – 2.84 (m, 1H; CH cyclopropane), 2.76 (ddd, *J* = 4.0, 6.8, 10.6 Hz, 1H; CH cyclopropane), 1.99 – 1.87 (m, 1H; CH_2 cyclopropane), 1.62 – 1.53 (m, 1H; CH_2 cyclopropane). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.1, 158.4, 155.6, 153.0, 132.0, 128.0, 127.4, 127.1, 123.8, 123.2, 114.0, 112.4, 112.4, 55.2, 29.8,

29.5, 19.2. IR ν 3004 (w), 2935 (w), 2835 (w), 1659 (s), 1613 (m), 1558 (s), 1516 (s), 1440 (m), 1397 (s), 1337 (m), 1294 (m), 1248 (s), 1180 (s), 1158 (s), 1140 (s), 1034 (s), 1001 (s), 932 (m), 888 (m), 830 (s), 801 (s), 749 (s), 688 (m). HRMS(ESI) calcd for $C_{19}H_{16}O_3^+$ (M+H) 293.1172, found 293.1172.

(2-Bromo-cyclohex-2-enyl)-trimethyl-silane (10)



Following a reported procedure,[9] bromoform (12 mL, 0.14 mmol, 1.0 equiv) was added to a thick slurry of potassium *tert*-butoxide (17 g, 0.15 mmol, 1.1 equiv) and cyclopentene (13 mL, 0.15 mmol, 1.1 equiv) in dry hexane (65 mL) over 30 min at 0 °C. The resulting yellow-brown suspension was warmed to 23 °C over 3 h and poured onto 300 g of ice. The mixture was extracted with PET (3x200 mL). The combined organic layers were washed with water (3x200 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Distillation (bp = 35-40 °C, p = 0.3 mbar gave cyclopropane **38** (23 g, 96 mmol, 69%) instead of the expected vinyl bromide **39** as a colorless oil. Quantitative conversion of **38** to the desired product **39** as a slightly brown oil was obtained by heating at 130 °C for 45 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.19 (m, 1H; alkene-H), 4.78 (m, 1H; CHBr), 2.09-2.38 (m, 6H; CH_2), 2.00 (m, 1H; CH_2), 1.76 (m, 1H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.7, 122.2, 53.9, 33.6, 27.4, 16.3. IR ν 2953 (w), 2935 (w), 2832 (w), 1634 (w), 1437 (w), 1319 (w), 1191 (m), 996 (w), 943 (w), 907 (s), 889 (m), 847 (w), 730 (s), 638 (m). ^{1}H NMR, ^{13}C NMR corresponded to the literature values.[10]

Following a reported procedure,[11] trichlorosilane (1.1 mL, 11 mmol, 1.1 equiv) was added to a solution of allyl bromide **39** (2.4 g, 10 mmol, 1.0 equiv), triethylamine (dist. over KOH, 1.4 mL, 10 mmol, 1.0 equiv) and CuCl (49 mg, 0.50 mmol, 0.050 equiv) in Et_2O (5 mL) at 15 °C. The resulting thick suspension was stirred at 23 °C for 4 h and filtered under nitrogen. The filter cake was washed with Et_2O (2x5 mL), the combined filtrates were cooled to 0 °C and MeMgBr (3 M in Et_2O, 13.3 mL, 40.0 mmol, 4.00 equiv) was added dropwise. The resulting red-green suspension was stirred for 1 h at 23 °C and poured onto sat. NH_4Cl solution (50 mL) at 0 °C. The mixture was extracted with Et_2O (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET) to yield allylsilane **10** (0.85 g, 3.7 mmol, 37%) contaminated by the corresponding methyl addition product **40** (0.45 g, 2.6 mmol, 26%) as colorless oils. Allyl silane **10** of 93% purity (0.71 g, 3.1 mmol, 31%) was obtained after stirring 1 h in HV (0.3 mbar). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.92 (td, *J* = 3.8, 1.6 Hz, 1H; alkene-H), 1.95-2.20 (m, 3H; CH_2), 1.82-1.94 (m, 1H; CH_2), 1.67-1.80 (m, 1H; CH_2), 1.47-1.64 (m, 2H; CH_2), 0.14 (s, 9 H, $SiCH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 126.1, 125.4, 35.3, 27.4, 27.3, 20.6, -1.0. IR ν 2934 (m), 2858 (w), 1637 (w), 1451 (w), 1249 (s), 1055 (w), 1031 (w), 986 (m), 940 (w), 919 (w), 836 (s), 798 (m), 733 (m), 692 (w), 615 (w). ^{1}H NMR, ^{13}C NMR corresponded to the literature values.[12]

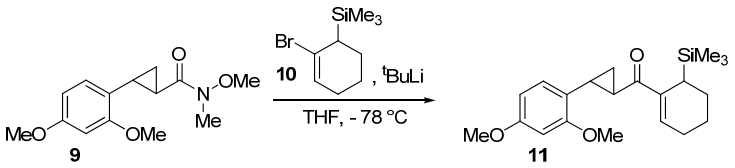
2-[2-(2,4-Dimethoxyphenyl)-1-cyclopropanecarbonyl]-3-trimethylsilyl-cyclohex-2-ene (11)

[9] Stevens, C. L.; Valicent.Ja *J. Am. Chem. Soc.* **1965**, *87*, 838.

[10] Banwell, M. G.; Cowden, C. J. *Aust. J. Chem.* **1994**, *47*, 2235.

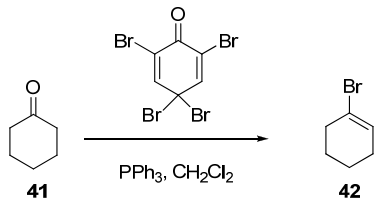
[11] Heerding, D. A.; Hong, C. Y.; Kado, N.; Look, G. C.; Overman, L. E. *J. Org. Chem.***1993**, *58*, 6947.

[12] Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.



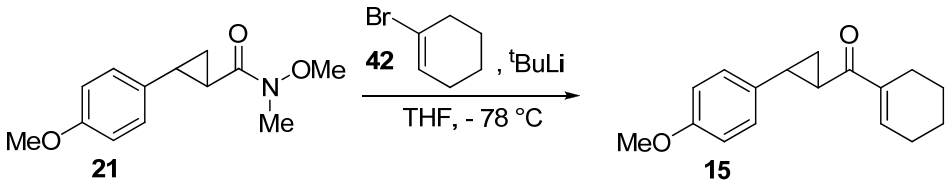
Amide **9** (363 mg, 1.37 mmol, 1.00 equiv) was added to vinyl bromide **10** (320 mg, 1.37 mmol, 1.00 equiv), following general procedure **4**. The deprotonation time was 30 min at -78°C and the reaction was quenched after 1 h to give **11** (250 mg, 0.70 mmol, 51%) as colorless oil without further purification. R_f 0.25 (PET/AcOEt 15:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (m, 1H; Ar-H), 6.82 (m, 1H; Ar-H), 6.42 (m, 1H; Ar-H), 6.39 (m, 1H; alkene-H), 3.79 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 2.59 (t, J = 9.8 Hz, 1H; CH cyclopropane), 2.45 – 2.32 (m, 2H; CH cyclopropane, CH_2 cyclohexene), 2.22 (m, 2H; CH_2 cyclohexene), 1.87 (m, 1H; CH_2 cyclopropane), 1.64– 1.49 (m, 5H, CH_2 cyclohexene), 1.37 (td, J = 3.9, 7.4 Hz, 0.7H; CH_2 cyclopropane, Diasteroisomer A), 1.33 – 1.24 (m, 0.3H; CH_2 cyclopropane, Diasteroisomer B), 0.94 – 0.76 (m, 1H; CHSi), 0.01 (s, 7H, $SiCH_3$ Diasteroisomer A), -0.02 (s, 2H; $SiCH_3$ Diasteroisomer B). From 0 ppm to 2.6 ppm we found several overlaps due to presence of 2 diastereoisomers. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.0, 159.5, 143.6, 135.8, 135.3, 126.8, 126.7, 121.6, 103.5, 103.8, 98.4, 98.3, 55.4, 55.1, 26.8, 26.5, 25.7, 25.7, 24.1, 24.0, 23.9, 23.8, 23.2, 23.2, 20.6, , 16.8, 16.1, -1.1. The excess of signals is due to presence of 2 diastereoisomers. IR ν 3003 (w), 2937 (w), 2836 (w), 1648 (m), 1614 (m), 1585 (w), 1509 (m), 1456 (w), 1436 (w), 1402 (m), 1291 (m), 1248 (m), 1208 (s), 1186 (m), 1159 (m), 1123 (w), 1034 (m), 990 (w), 955 (m), 920 (w), 835 (s), 796 (w), 752 (w), 731 (w). HRMS(ESI) calcd for $C_{21}H_{30}O_3Si^+$ (M+H) 359.2037, found 359.2044.

1-Bromocyclohexene (42)



Following a reported procedure,[13] a mixture of cyclohexenone (distilled, 0.50 g, 5.1 mmol, 1.0 equiv), triphenylphosphine (3.2 g, 12 mmol, 2.4 equiv) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone (4.9 g, 12 mmol, 2.4 equiv) was refluxed in CH_2Cl_2 (15 mL) for 18 h. The crude mixture was filtered over SiO_2, washed with CH_2Cl_2 and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/Et_2O 100:1) to yield 1-bromocyclohexene **(42)** (354 mg, 90% pure by ^{1}HNMR, 1.98 mmol, 39%). R_f 0.80 PET/Et_2O 100:1, $KMNO_4$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.03 (m, 1 H, alkene H), 2.36-2.48 (m, 2 H, CH_2), 2.02-2.12 (m, 2 H, CH_2), 1.68-1.79 (m, 2 H, CH_2), 1.54-1.67 (m, 2 H, CH_2) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 128.9, 122.3, 35.2, 27.4, 24.5, 21.1. ^{1}H NMR, ^{13}C NMR corresponded to the literature values.[13]

Cyclohex-1-enyl-[2-(4-methoxy-phenyl)-cyclopropyl]-methanone (15)

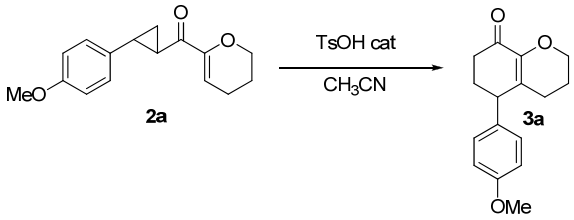


([13]) Matveeva, E. D.; Feshin, D. B.; Zefirov, N. S. *Russ. J. Org. Chem.* **2001**, *37*, 52.

Amide **21** (445 mg, 1.68 mmol, 1.00 equiv) was added to vinyl bromide **42** (300 mg, 90% pure, 1.68 mmol, 1.00 equiv), following general procedure **4**. The deprotonation time was 30 min at -78°C and the reaction was quenched after 2 h to give **15** (275 mg, 1.07 mmol, 64%) as a colorless solid after purification on column chromatography (PET/AcOEt 10:1). (R_f 0.25 (PET/AcOEt 15:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (d, J = 8.8 Hz, 2 H, Ar H), 6.99 (br m, 1 H, alkene H), 6.83 (d, J = 8.8 Hz, 2 H, Ar H), 3.79 (s, 3 H, OCH_3), 2.51 (m, 1 H, cyclopropane H), 2.45 (m, 1 H, cyclopropane H), 2.21-2.33 (m, 4 H, cyclohexene CH_2), 1.57-1.73 (m, 5 H, Cyclohexene and cyclopropane CH_2), 1.30 (ddd, J = 8.1, 6.5, 4.0 Hz, 1 H, cyclopropane CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.1, 158.2, 139.8, 139.7, 132.9, 127.2, 113.8, 55.3, 28.3, 27.5, 26.1, 23.5, 21.9, 21.6, 18.2. IR ν 3004 (w), 2935 (m), 2934 (m), 2863 (w), 2862 (w), 2836 (w), 2835 (w), 1650 (s), 1649 (s), 1517 (s), 1405 (m), 1250 (s), 1205 (m), 1037 (w), 1031 (w), 917 (w), 837 (w), 741 (w), 736 (w). HRMS(ESI) calcd for $C_{17}H_{21}O_2^+$ (M+H) 257.1536, found 257.1543.

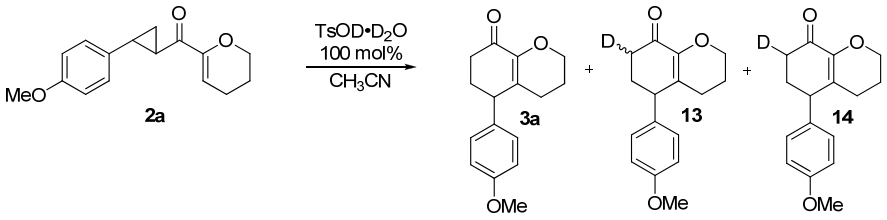
4 Cyclization

5-(4-Methoxyphenyl)-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (3a)



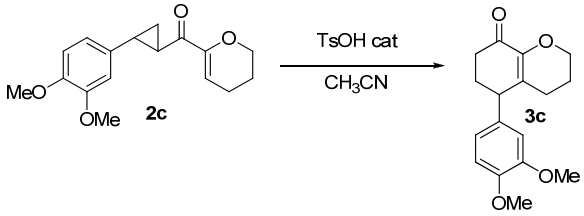
The reaction was carried out following general procedure **5**, starting from cyclopropane **2a** (103 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 18 h. Purification by flash chromatography (PET/AcOEt, 4:1) afforded **3a** (72 mg, 0.28 mmol, 70 %) as yellow oil. R_f 0.35 (PET/AcOEt 1:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (d, J = 8.6 Hz, 2H; Ar-H), 6.88 (d, J = 8.6 Hz, 2H; Ar-H), 4.20 – 3.99 (m, 2H; CH_2O), 3.81 (s, 3H, OCH_3), 3.58 (t, J = 5.2 Hz, 1H;CH-Ar), 2.59 – 2.47 (m, 1H; CH_2), 2.45 – 2.27 (m, 2H; CH_2), 2.03 – 1.90 (m, 3H; CH_2), 1.85 (d, J = 6.0 Hz, 2H; CH_2). ^{1}H NMR (benzene-d^6, 400 MHz) δ 6.83-6.77 (m, 2H, Ar-H), 6.76-6.70 (m, 2H; Ar-H), 3.75-3.57 (m, 2H; CH_2O), 3.33 (s, 3H, OCH_3), 3.02 (dd, J = 6.00, 5.29 Hz, 1H, CH-Ar), 2.37 (ddd, J = 16.61, 9.59, 4.50 Hz, 1H, CH_2-ketone), 2.14 (ddd, J = 16.58, 8.04, 4.49 Hz, 1H, CH_2-ketone), 1.85 (tdd, J = 13.29, 9.57, 4.65 Hz, 1H, CH_2), 1.62-1.49 (m, 2H, CH_2), 1.45-1.35 (m, 1H, CH_2), 1.32-1.20 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 158.5, 146.8, 133.3, 132.1, 128.9, 114.1, 65.8, 55.2, 45.0, 34.9, 30.9, 25.1, 21.8. IR ν 2934 (m), 2870 (w), 1683 (s), 1612 (w), 1511 (s), 1463 (w), 1385 (w), 1293 (w), 1247 (s), 1180 (m), 1154 (m), 1085 (w), 1035 (m), 986 (w), 926 (w), 833(m). HRMS(ESI) calcd for $C_{16}H_{18}O_3^+$ (M+H) 259.1329, found 259.1323.

Deuterium Labeling Experiment



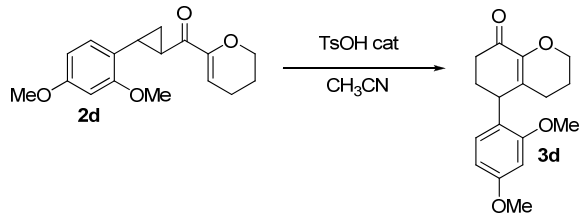
The reaction was carried out following general procedure **5**, starting from cyclopropane **2a** (33 mg, 0.13 mmol, 1.0 equiv) and deuterated tosic acid monohydrate (23 mg, 0.13 mmol, 1.0 equiv). The reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 4:1) afforded a mixture of 3a, 13 and 14 (20 mg, 0.078 mmol, 61 %) as yellow oil. R_f 0.35 (PET/AcOEt 1:1, Anisaldehyde).). ^{1}H NMR (benzene-d^6, 400 MHz) δ 6.83-6.77 (m, 2H, Ar-H), 6.76-6.70 (m, 2H; Ar-H), 3.75-3.57 (m, 2H; CH_2O), 3.33 (s, 3H, OCH_3), 3.02 (m, 1H, CH-Ar), 2.37 (ddd, *J* = 16.61, 9.59, 4.50 Hz, 0.6H, CH_2-ketone), 2.14 (ddd, *J* = 16.58, 8.04, 4.49 Hz, 0.6H, CH_2-ketone), 1.85 (m, 1H, CH_2), 1.62-1.49 (m, 2H, CH_2), 1.45-1.35 (m, 1H, CH_2), 1.32-1.20 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ193.33, 193.29, 193.24, 158.6, 146.8, 133.36, 133.331, 133.30, 133.26, 132.16, 132.13, 129.0, 114.1, 65.9, 55.3, 45.06, 45.03, 45.00, 44.97, 34.9, 34.5 (t, *J* = 19.5 Hz), 30.91, 30.85, 30.81, 30.74, 29.7, 25.1, 21.8. HRMS(ESI) calcd for $C_{16}H_{18}NaO_3^+$ (M+Na) 281.1148, found 281.1141 (87%), calcd for $C_{16}H_{17}DNaO_3^+$ (MD+Na) 282.1211, found 282.1205 (100%), calcd for $C_{16}H_{16}D_2NaO_3^+$ (MD_2+Na) 283.1274, found 283.1278 (70%).

5-(3,4-Dimethoxyphenyl)-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (3c)



The reaction was performed following general procedure **5**, starting from cyclopropane **2c** (115 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 5 h to give **3c** (115 mg, 0.400 mmol, 100 %) as yellow oil without further purification. R_f 0.25 (PET/AcOEt 1:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82 (d, *J* = 8.2 Hz, 1H; Ar-H), 6.76 – 6.68 (m, 2H; Ar-H), 4.17 – 4.02 (m, 2H; CH_2O), 3.87 (s, 3H; OCH_3), 3.86 (s, 3H; OCH_3), 3.57 (t, *J* = 5.3 Hz, 1H; CH Ar) 2.54 (ddd, *J* = 4.3, 9.5, 16.2 Hz, 1H; CH_2), 2.46 – 2.28 (m, 2H; CH_2), 2.03 – 1.92 (m, 3H; CH_2), 1.91 – 1.78 (m, 2H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.1, 149.1, 146.7, 144.9, 133.7, 131.9, 119.8, 111.1, 65.8, 55.8, 55.8, 45.3, 34.9, 30.7, 25.0, 21.7. IR ν 2936 (w), 2871 (w), 2835 (w), 1731 (w), 1678 (s), 1629 (w), 1592 (w), 1515 (s), 1464 (m), 1450 (w), 1418 (w), 1385 (w), 1279 (w), 1265 (m), 1248 (m), 1233 (m), 1182 (m), 1139 (s), 1085 (w), 1026 (s), 987 (m), 913 (m), 851 (w), 812 (w), 728 (s). HRMS(ESI) calcd for $C_{17}H_{20}O_4^+$ (M+H) 289.1434, found 289.1420.

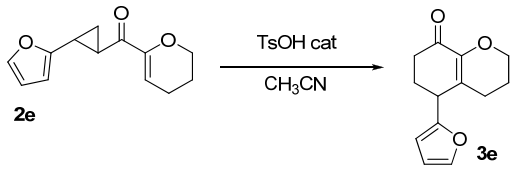
5-(2,4-Dimethoxyphenyl)-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (3d)



The cyclization was achieved following general procedure **5**, starting from cyclopropane **2d** (115 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 10 min to give **3d** (115 mg, 0.400 mmol, 100 %) as yellow oil without further purification. R_f 0.40 (PET/AcOEt 1:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82 (d, *J* = 8.2 Hz, 1H; Ar-H), 6.77 – 6.68 (m, 2H; Ar-H), 4.19 – 4.01 (m, 2H; CH_2O), 3.87 (s, 3H; OCH_3), 3.86 (s, 3H; OCH_3), 3.57 (t, *J* = 5.3 Hz, 1H;

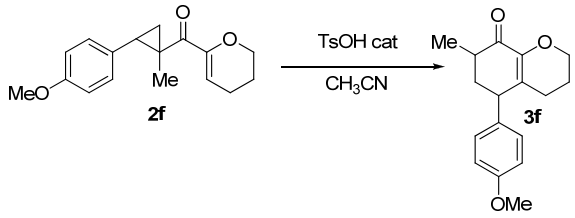
CH Ar), 2.54 (ddd, J = 4.3, 9.5, 16.2 Hz, 1H; CH_2), 2.46 – 2.28 (m, 2H; CH_2), 2.04 – 1.92 (m, 3H; CH_2), 1.91 – 1.77 (m, 2H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.8, 159.8, 158.3, 147.0, 132.8, 128.4, 120.9, 103.7, 98.8, 65.8, 55.3, 55.2, 38.3, 34.9, 28.2, 24.9, 21.9. IR ν 2961 (w), 2937 (w), 2837 (w), 1674 (m), 1612 (w), 1587 (w), 1505 (w), 1465 (w), 1438 (w), 1419 (w), 1388 (w), 1293 (w), 1259 (w), 1208 (m), 1158 (m), 1115 (w), 1087 (w), 1036 (w), 986 (w), 907 (s), 838 (w), 827 (w), 726 (s), 648 (m). HRMS(ESI) calcd for $C_{17}H_{20}O_4^+$ (M+H) 289.1434, found 289.1444.

5-(Furan-2-yl)-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (3e)



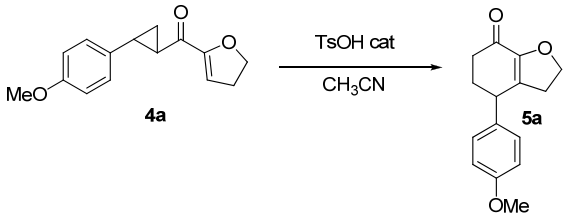
The cyclization was achieved following general procedure **6**, starting from cyclopropane **2e** (87.3 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 2 h. Purification by flash chromatography (PET/AcOEt, 2:8) afforded3 (44 mg, 0.20 mmol, 50 %) as yellow oil. R_f 0.10 (PET/AcOEt 8:2, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (s, 1H; Ar-H), 6.36 – 6.26 (m, 1H; Ar-H), 6.07 (d, J = 3.1 Hz, 1H; Ar-H), 4.13 – 4.01 (m, 2H; CH_2O), 3.68 (t, J = 4.9 Hz, 1H; CH Ar), 2.68 – 2.51 (m, 1H; CH_2), 2.47 – 2.35 (m, 1H; CH_2), 2.32 – 2.13 (m, 2H; CH_2), 2.10 (t, J = 6.4 Hz, 2H; CH_2), 1.86 (dq, J = 3.6, 6.6 Hz, 2H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.8, 154.4, 146.5, 142.0, 130.0, 110.2, 106.7, 65.9, 39.2, 35.1, 29.6, 24.8, 21.8. IR ν 2933 (w), 2874 (w), 1685 (m), 1635 (w), 1505 (w), 1385 (w), 1289 (w), 1146 (w), 1087 (w), 1043 (w), 1009 (w), 985 (w), 911 (m), 854 (w), 810 (w), 730 (s). HRMS(ESI) calcd for $C_{13}H_{14}O_3^+$ (M+H) 219.1016, found 219.1007.

5-(4-Methoxyphenyl)-7-methyl-3,4,6,7-tetrahydro-2*H*-chromen-8(5*H*)-one (3f)



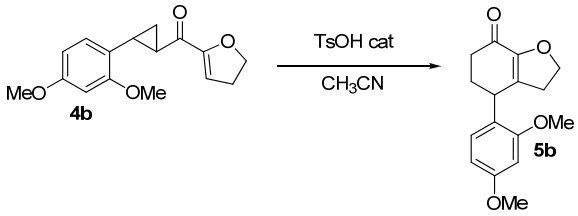
The reaction was carried out following general procedure **5**, starting from cyclopropane **2f** (64.0 mg, 0.235 mmol, 1.00 equiv) and tosic acid (9.0 mg, 0.047 mmol, 0.20 equiv). The reaction was quenched after 1 h. Purification by flash chromatography (PET/AcOEt, 8/2) afforded **3f** (64.0 mg, 0.235 mmol, 100 %, 5:1 mixture of diastereoisomers) as yellow oil. R_f 0.15 (PET/AcOEt 8:2, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) (Major diastereoisomer) δ 7.10 (d, J = 8.4 Hz, 2H; Ar-H), 6.86 (d, J = 8.5 Hz, 2H; Ar-H), 4.26 (d, J = 8.8 Hz, 1H; CH_2O), 3.95 – 3.81 (m, 1H; CH_2O), 3.79 (s, 3H; OCH_3), 3.55 (d, J = 7.3 Hz, 1H; CH Ar), 2.64 – 2.40 (m, 1H; CH_2), 2.14 (m, 1H; CH_2), 1.79 (m, 4H; CH_2), 1.15 (m, 3H; CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.4, 158.4, 146.3 135.1, 131.6, 129.0, 128.5 114.0, 113.6, 65.7, 55.2, 46.0, 41.3, 40.3, 25.0, 21.7, 14.9. IR ν 2961 (w), 2932 (w), 2870 (w), 2836 (w), 1729 (w), 1682 (s), 1623 (m), 1611 (w), 1584 (w), 1512 (s), 1458 (w), 1444 (w), 1385 (w), 1272 (m), 1250 (s), 1178 (m), 1149 (s), 1093 (w), 1079 (w), 1035 (m), 990 (m), 919 (w), 855 (w), 833 (m), 732 (m). HRMS(ESI) calcd for $C_{17}H_{20}O_3^+$ (M+H) 273.1485, found 273.1490.

4-(4-Methoxyphenyl)-2,3,5,6-tetrahydrobenzofuran-7(4*H*)-one (5a)



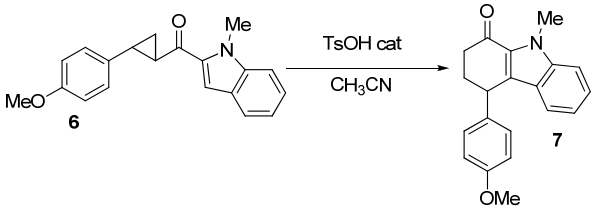
The reaction was performed following general procedure **5**, starting from cyclopropane derivate **4a** (98 mg, 0.40 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 36 h. Purification by flash chromatography (PET/AcOEt, 7:3) afforded **5a** (15 mg, 0.060 mmol, 15 %) as yellow oil. R_f 0.40 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR (CDCl3, 400 MHz) δ 7.12 (d, *J* = 8.5 Hz, 2H; Ar-H), 6.89 (d, *J* = 8.5 Hz, 2H; Ar-H), 4.50 – 4.37 (m, 2H; CH_2O), 3.81 (s, 3H; OCH_3), 3.75 (m, 1H; CH Ar), 2.65 (t, *J* = 9.6 Hz, 2H; CH_2), 2.59 – 2.50 (m, 1H; CH_2), 2.49 – 2.31 (m, 2H; CH_2), 2.11 – 1.98 (m, 1H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.3, 158.7, 150.2, 136.9, 133.1, 128.6, 114.2, 69.3, 55.3, 41.2, 36.5, 33.1, 32.8. IR ν 2951 (w), 2934 (w), 2838 (w), 1767 (w), 1676 (s), 1641 (w), 1611 (m), 1512 (s), 1463 (w), 1443 (w), 1395 (w), 1340 (w), 1302 (w), 1244 (s), 1178 (m), 1148 (w), 1102 (s), 1033 (m), 1003 (m), 935 (w), 874 (w), 834 (m), 771 (w), 736 (w). HRMS(ESI) calcd for $C_{15}H_{16}O_3^+$ (M+H) 245.1172, found 245.1171.

4-(2,4-Dimethoxyphenyl)-2,3,5,6-tetrahydrobenzofuran-7(4*H*)-one (5b)



The reaction was carried out following general procedure **6** from cyclopropane **4b** (110 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 15 min to give **5b** (104 mg, 0.380 mmol, 95 %) without further purification as yellow oil. R_f 0.30 (PET/AcOEt 7:3, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (d, *J* = 8.3 Hz, 1H; Ar-H), 6.49 (s, 1H; Ar-H), 6.45 (d, *J* = 8.3 Hz, 1H; Ar-H), 4.42 (td, *J* = 3.0, 9.6 Hz, 2H; CH_2O), 4.13 (dd, *J* = 5.2, 6.4 Hz, 1H; CH Ar), 3.82 (s, 3H; OCH_3), 3.80 (s, 3H; OCH_3), 2.67 (t, *J* = 9.6 Hz, 2H; CH_2), 2.53 – 2.34 (m, 2H; CH_2), 2.27 (d, *J* = 4.9 Hz, 1H; CH_2), 2.08 (d, *J* = 6.7 Hz, 1H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.1, 160.3, 158.4, 150.8, 138.1, 128.8, 121.2, 104.4, 99.3, 69.6, 55.7, 55.7, 36.7, 34.9, 33.2, 31.1. IR ν 2958 (w), 2838 (w), 1674 (m), 1612 (m), 1587 (m), 1506 (m), 1466 (m), 1439 (m), 1419 (m), 1293 (m), 1262 (m), 1208 (m), 1159 (m), 1102 (m), 1035 (m), 906 (s), 839 (m), 726 (s), 648 (m). HRMS(ESI) calcd for $C_{16}H_{18}O_4^+$ (M+H) 275.1278, found 275.1292.

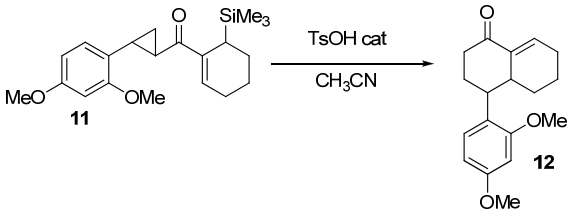
4-(4-Methoxyphenyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (7)



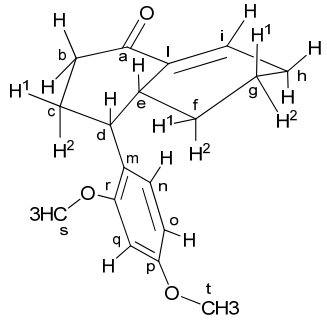
Following general procedure **5**, tosic acid (15 mg, 0.08 mmol, 0.2 equiv) was added to a cyclopropane **6** (122 mg, 0.400 mmol, 1.00 equiv). The reaction was quenched after 3 h and 30 min to give **7** (122 mg, 0.400

mmol, 100%) as a yellow oil without further purification. R_f 0.30 (PET/AcOEt 8:2, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 – 7.30 (m, 2H; Ar-H), 7.13 (d, *J* = 8.6 Hz, 2H; Ar-H), 7.00 – 6.90 (m, 2H; Ar-H), 6.84 (d, *J* = 8.6 Hz, 2H; Ar-H), 4.45 (dd, *J* = 4.9, 7.5 Hz, 1H; CH Ar), 4.13 (s, 3H; NCH_3), 3.80 (s, 3H; OCH_3), 2.76 – 2.56 (m, 2H; CH_2), 2.51 (ddd, *J* = 4.6, 9.2, 12.3 Hz, 1H; CH_2), 2.25 (ddd, *J* = 4.5, 11.1, 17.4 Hz, 1H; CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.7, 158.8, 140.3, 135.9, 131.1, 131.0, 129.5, 126.9, 124.9, 122.9, 120.5, 114.3, 110.6, 55.7, 40.1, 38.4, 35.2, 32.0. IR ν 3058 (w), 2938 (w), 2833 (w), 1654 (s), 1612 (m), 1510 (s), 1471 (m), 1429 (w), 1410 (w), 1375 (w), 1347 (w), 1243 (s), 1203 (w), 1176 (m), 1072 (w), 1035 (m), 909 (m), 833 (m), 730 (s), 648 (w). HRMS(ESI) calcd for $C_{20}H_{19}NO_2^+$ (M+H) 306.1489, found 306.1478.

4-(2,4-Dimethoxyphenyl)-3,4,4a,5,6,7-hexahydronaphthalen-1(2*H*)-one (12)



The reaction was performed following general procedure **6**, starting from cyclopropane **11** (143 mg, 0.400 mmol, 1.00 equiv) and tosic acid (15 mg, 0.080 mmol, 0.20 equiv). The reaction was quenched after 25 minutes. Purification by flash chromatography (PET/AcOEt, 8:2) afforded **12** (63 mg, 0.22 mmol, 55 %) as colorless oil.

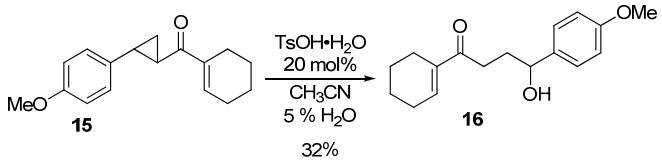


R_f 0.30 (PET/AcOEt 8:2, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06 (d, *J* = 8.0 Hz, 1H; H^n), 6.79 (br s, 1H; H^i), 6.48 (d, *J* = 7.7 Hz, 2H; H^l and H^m), 3.81 (s, 3H; H^s or H^t), 3.80 (s, 3H; H^s or H^t), 3.03 (m, 1H; H^d), 2.74 – 2.60 (m, 1H; H^b), 2.61 – 2.54 (m, 1H; H^e), 2.54 – 2.40 (m, 1H; H^b), 2.20 (m, 2H; H^h), 2.04 (m, 1H; H^{c1}), 2.01 – 1.90 (m, 1H; H^{c2}), 1.67 (m, 1H; H^{g2}), 1.61 – 1.47 (m, 1H; H^{f2}), 1.36 (m, 1H; H^{g1}), 1.10 (m, 1H; H^{f1}). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.1 (a), 159.0 (r), 158.2 (p), 139.7 (l), 136.8 (i), 127.5 (n), 124.8 (m), 104.3 (o), 98.5 (q), 55.4 (s or t), 55.3 (s or t), 42.4 (d), 40.4 (e), 39.2 (b), 29.9 (c), 27.8 (f), 26.2 (h), 21.4 (g). IR ν 3000 (w), 2935 (m), 2861 (w), 2836 (w), 1686 (s), 1613 (s), 1587 (m), 1507 (s), 1465 (m), 1456 (m), 1420 (w), 1328 (w), 1296 (m), 1268 (m), 1209 (s), 1158 (m), 1036 (m), 927 (w), 836 (w), 737 (w). HRMS(ESI) calcd for $C_{18}H_{22}O_3^+$ (M+H) 287.1647, found 287.1636.

Further analytical data: COESY, NOESY and HSQC.

Important signal for NOESY : H^e-H^d(s); H^e-H^{f1}(m); H^d-H^{c1}(s).

1-Cyclohex-1-enyl-4-hydroxy-4-(4-methoxy-phenyl)-butan-1-one (16)



A solution of cyclopropane 15 (81 mg, 0.32 mmol, 1.0 equiv) and tosic acid monohydrate (59 mg, 0.32 mmol, 1.0 equiv) in acetonitrile (8 mL) and water (0.4 mL) was stirred at RT for 36 h. The solution was quenched with $NaHCO_3$ (10 mL) and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (2x10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography (PET/AcOEt, 4:1-2:1) afforded **16** (27 mg, 0.099 mmol, 32 %) as yellow oil. (***R*****f** 0.20 (PET/AcOEt 4:1, Anisaldehyde). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.30 (m, 2 H, Ar-H), 6.83-6.92 (m, 3 H, Ar-H and alkene-H), 4.69 (br m, 1 H, C*H*OH), 3.80 (s, 3 H, OCH_3), 2.75 (td, *J* = 7.0, 1.0 Hz, 2 H, ketone-CH_2), 2.47 (br s, 1 H, OH), 2.17-2.29 (m, 4 H, cyclohexene-CH_2), 2.05 (q, *J* = 6.9 Hz, 2 H, C*H*$_2$CHOH), 1.54-1.68 (m, 4 H, cyclohexene-CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.7, 158.9, 140.3, 139.0, 136.6, 126.9, 113.8, 73.40, 55.3, 33.4, 33.3., 26.1, 23.1, 21.9, 21.5. IR ν 3447 (br w), 2932 (m), 2860 (w), 1663 (m), 1614 (m), 1514 (s), 1458 (w), 1302 (w), 1247 (s), 1175 (m), 1034 (s), 914 (w), 832 (m), 734 (w). HRMS(ESI) calcd for $C_{17}H_{22}NaO_3^+$ (M+Na) 297.1461, found 297.1452.

5. Kinetic Measurements

5.1 Methods and Formula

NMR-Method for the Monitoring of the Formal Homo-Nazarov Cyclization

Substrate **2a** (6.00 mg, 0.00232 mmol, 1.00equiv) was dissolved in CD_3CN (0.5 mL) at 23 °C under nitrogen in a NMR tube. A solution of the desired amount of tosic acid in CD_3CN (0.15 mL) was then added and the tube put in the spectrometer as fast as possible (time set to zero at this point). The reaction was monitored by *^{1}H*-NMR at 400 MHz. The reaction was examined with 0.1, 0.2, 0.3 and 0.4 equiv tosic acid and 0.4 equiv deuterated tosic acid. The decrease of the concentration of **2a** was monitored via the decrease of the integral of the alkene proton peak between 6.0383 and 6.0022 ppm, using the internal CH_3CN signal as standard. The concentration of product 3a was monitored via the increase of the integral of the benzylic proton between 3.6454 and 3.6050 ppm. This signal was increase further by a factor 1.33 (part of the signal was dropped in the integration due to impurity interference, the correction factor was obtained by integrating the missing area on a pure sample) and 1.09 (difference of integration between the two observed signal for a separately prepared 1:1 solution). Better results were obtained with the alkene proton, as the baseline was more stable in this region of the spectra. Spectra were taken every 36.5 s with one single scan.

Statistical Methods and Formula[14]

Reaction Rate

The initial rates r of the reactions were determined using standard linear regression programs (Excel) applied on the linear region of the concentration curves (4.25 min). The standard deviation and the confidence interval of the data were calculated using following formula:

([14]) Meister, E. *Grundpraktikum Physikalische Chemie*; vdf Hochschulverlag AG: Zürich, 2000.

Standard deviation of the rate: $$s_r^2 = \frac{n}{n \cdot \sum_{i=1}^{n} t_i^2 - (\sum_{i=1}^{n} t_i)^2} \cdot \sum_{i=1}^{n} \left(c_i - I - r \cdot t_i\right)^2 \cdot \frac{1}{n-2}$$;

Confidence interval (95%) of the rate: $$v_r = t_s \cdot \frac{s_r}{\sqrt{n}}$$;

Whereas n is the amount of data points measured, t is the time of measurement after the addition of acid, c is the measured concentration of **2a**, r is the calculated reaction rate, I is the calculate intercept of the curve, t_s is the student-t factor corresponding to 95% probability and a degree of freedom of n-2.

Van't Hoff **Equation**

Van't Hoff Equation: $$y = \log r = O \cdot \log c + I = a \cdot \log c + b$$;

Standard deviation, confidence interval for y values: $$s_{yi} = \frac{s_{ri}}{Ln(10) \cdot r_i}, \quad v_{yi} = \frac{v_{ri}}{Ln(10) \cdot r_i}$$;

Standard deviation of the reaction order: $$s_O = s_a = \frac{\sum_{i=1}^{m} \frac{1}{s_{yi}^2}}{\sum_{i=1}^{m} \frac{1}{s_{yi}^2} \cdot \sum_{i=1}^{m} \frac{x_i^2}{s_{yi}^2} - (\sum_{i=1}^{m} \frac{x_i}{s_{yi}^2})^2}, x_i = \log c_i$$;

Confidence interval (95%) of the reaction order: $$v_O = v_a = t_s \cdot \frac{s_a}{\sqrt{m}}$$;

Correlation factor R: $$\frac{\sum_{i=1}^{m} \frac{1}{s_{yi}^2} \cdot \sum_{i=1}^{m} \frac{x_i y_i}{s_{yi}^2} - \sum_{i=1}^{m} \frac{x_i}{s_{yi}^2} \cdot \sum_{i=1}^{m} \frac{y_i}{s_{yi}^2}}{\sqrt{\sum_{i=1}^{m} \frac{1}{s_{yi}^2} \cdot \sum_{i=1}^{m} \frac{x_i^2}{s_{yi}^2} - \left(\sum_{i=1}^{m} \frac{x_i}{s_{yi}^2}\right)^2} \cdot \sqrt{\sum_{i=1}^{m} \frac{1}{s_{yi}^2} \cdot \sum_{i=1}^{m} \frac{y_i^2}{s_{yi}^2} - \left(\sum_{i=1}^{m} \frac{y_i}{s_{yi}^2}\right)^2}}$$

Whereas r is the calculated reaction rate with standard deviation s_r and confidence interval v_r, O is the reaction order with standard deviation s_O and confidence interval v_O, c is the concentration of the examined reagent, m is the amount of data points measured, R is the correlation factor, t_s is the student-t factor corresponding to 95% probability and a degree of freedom of n-2.

5.2 Graphical Representation of the Data

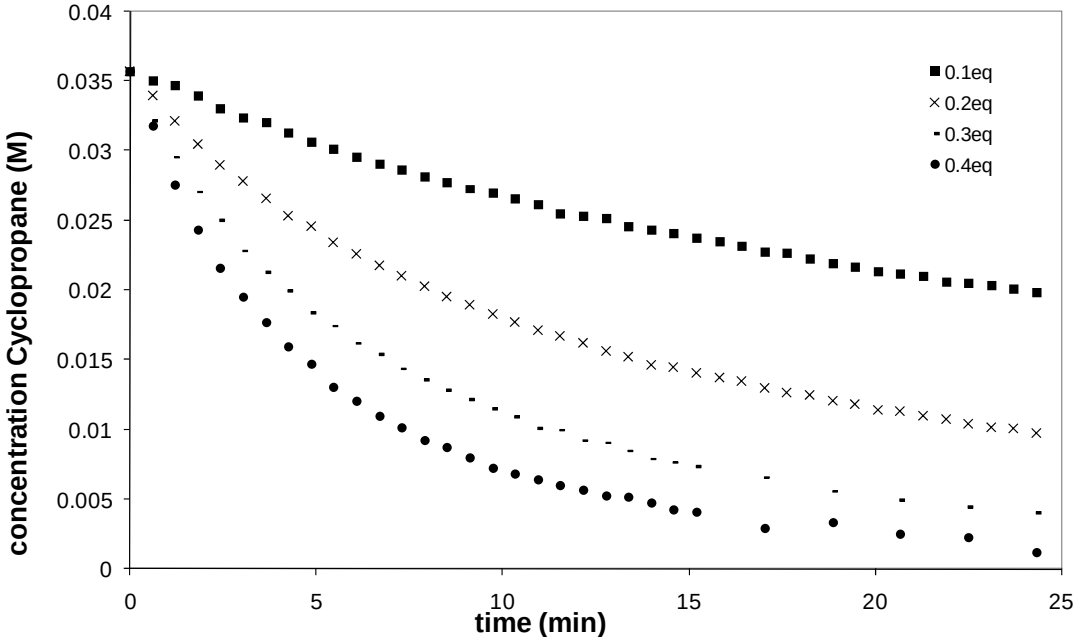


Figure S1. Influence of the concentration of tosic acid on the reaction rate of the starting material **2a**.

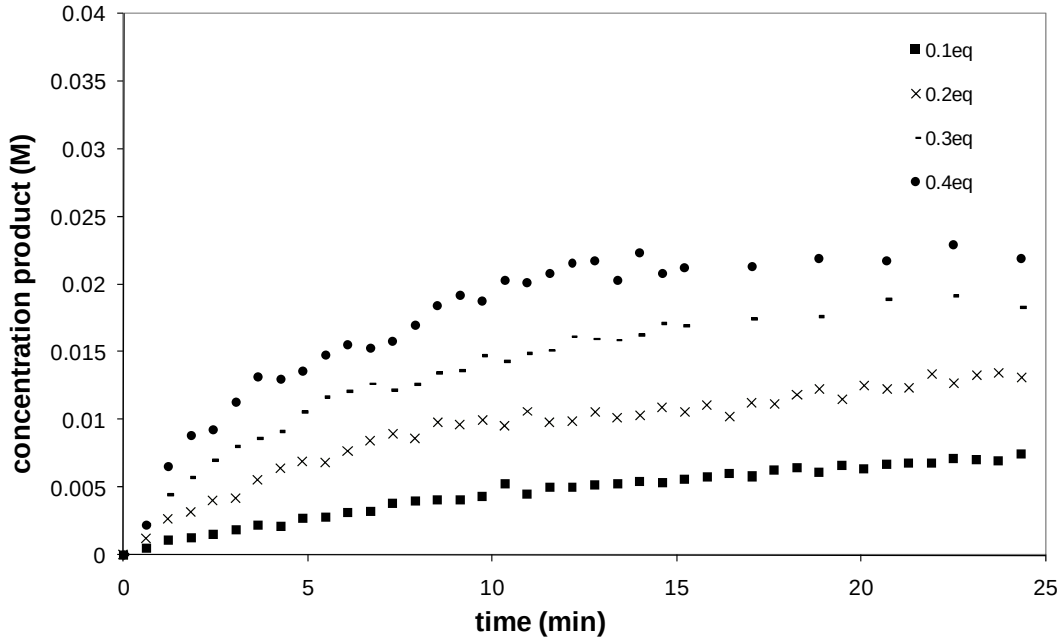


Figure S2. Influence of the concentration of tosic acid on the formation of product **3a**.

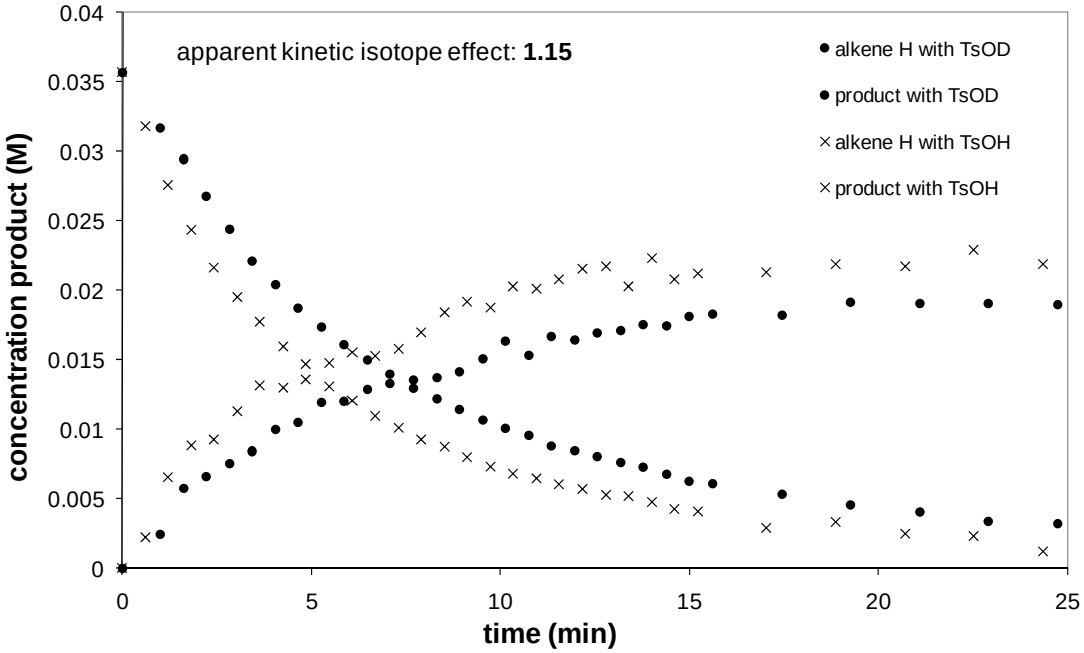


Figure S3. Comparison of tosic acid and deuterated tosic acid: kinetic isotope effect?

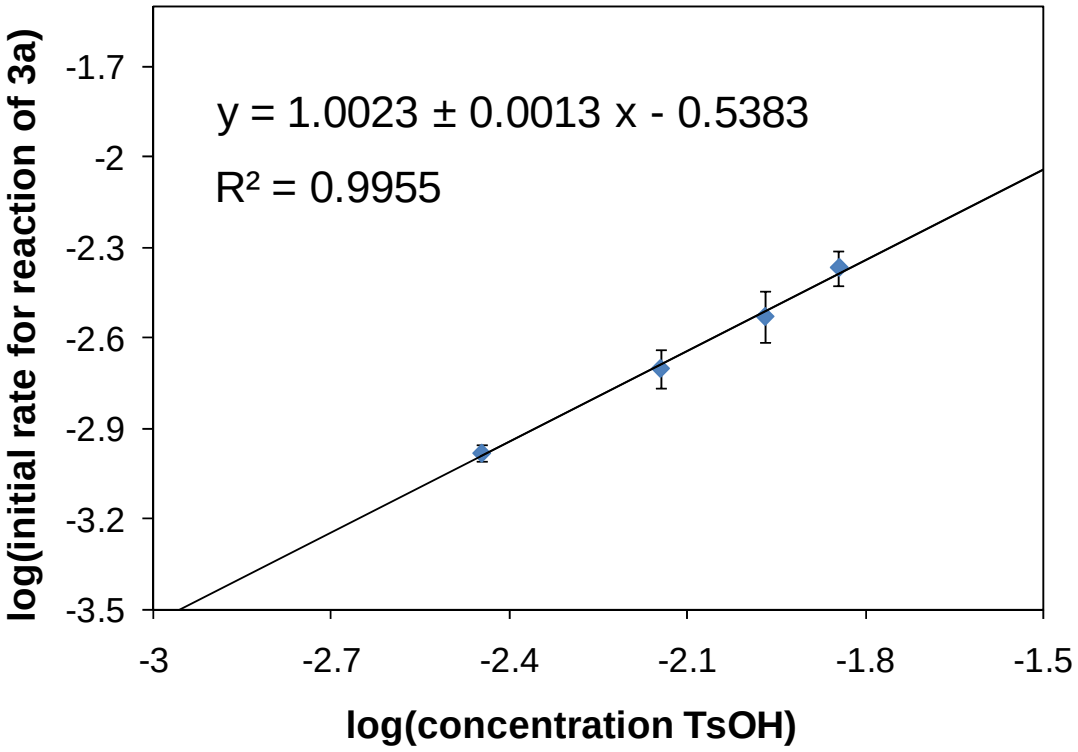


Figure S4. Determination of the rate order using Van't Hoff plot.

6.1 Important Spectra for Analysis of the Reaction

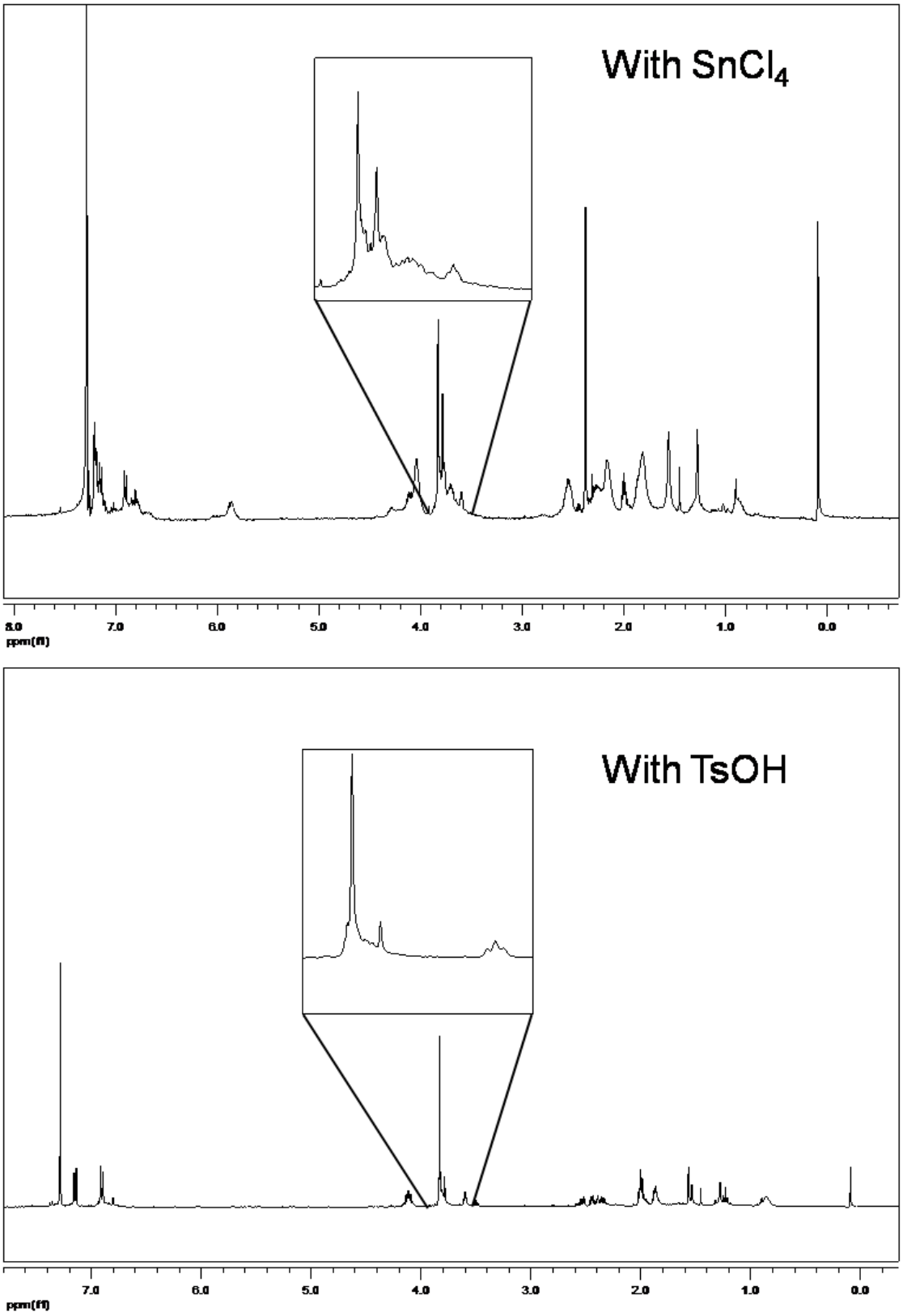


Figure S5. Comparison of the crude NMR of the reaction of **2a** with $SnCl_4$ and TsOH.

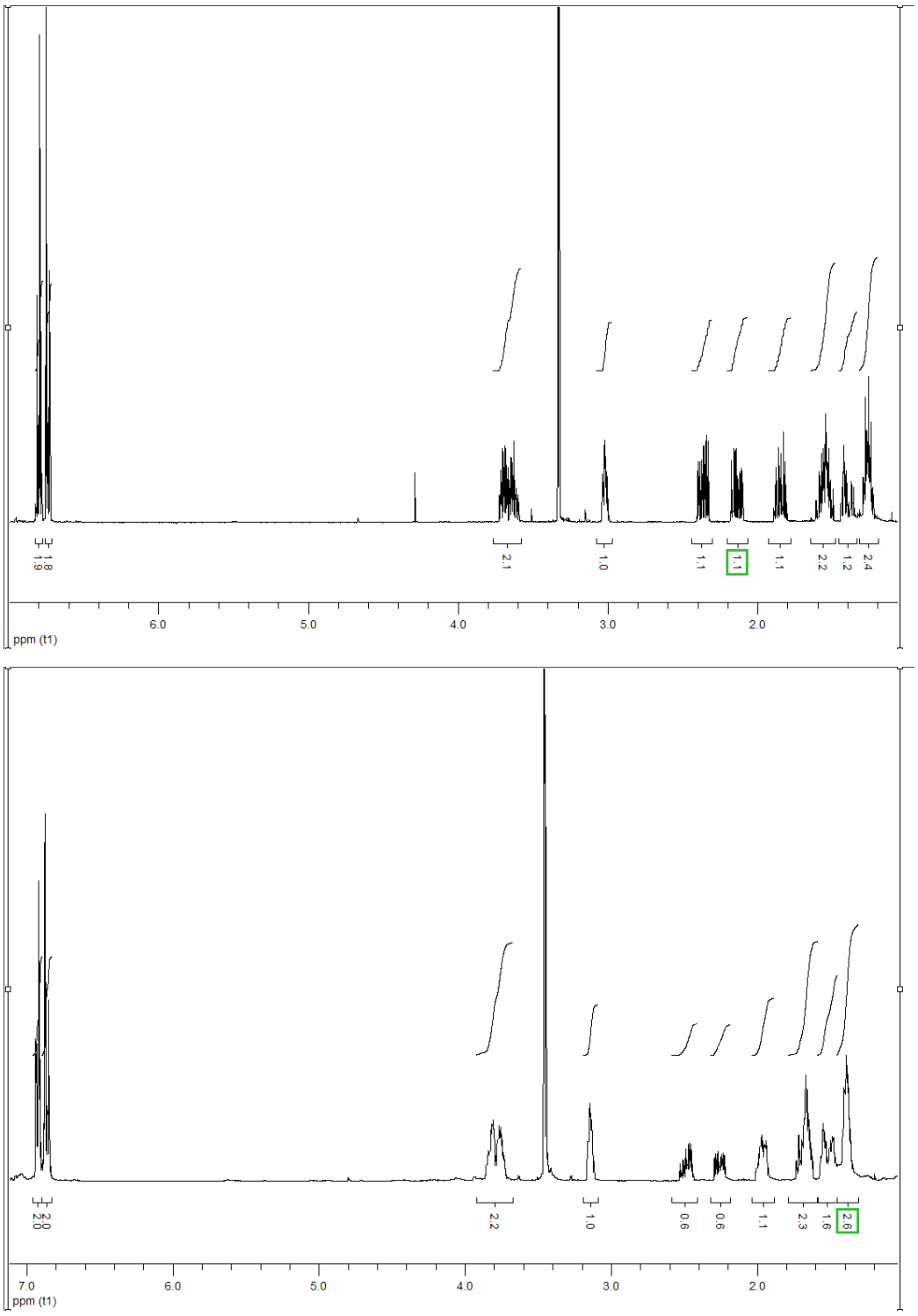


Figure S6 ^{1}H NMR spectra in benzene-*d6* of cyclization product **3a** obtained using TsOH (top) and TsOD (bottom).

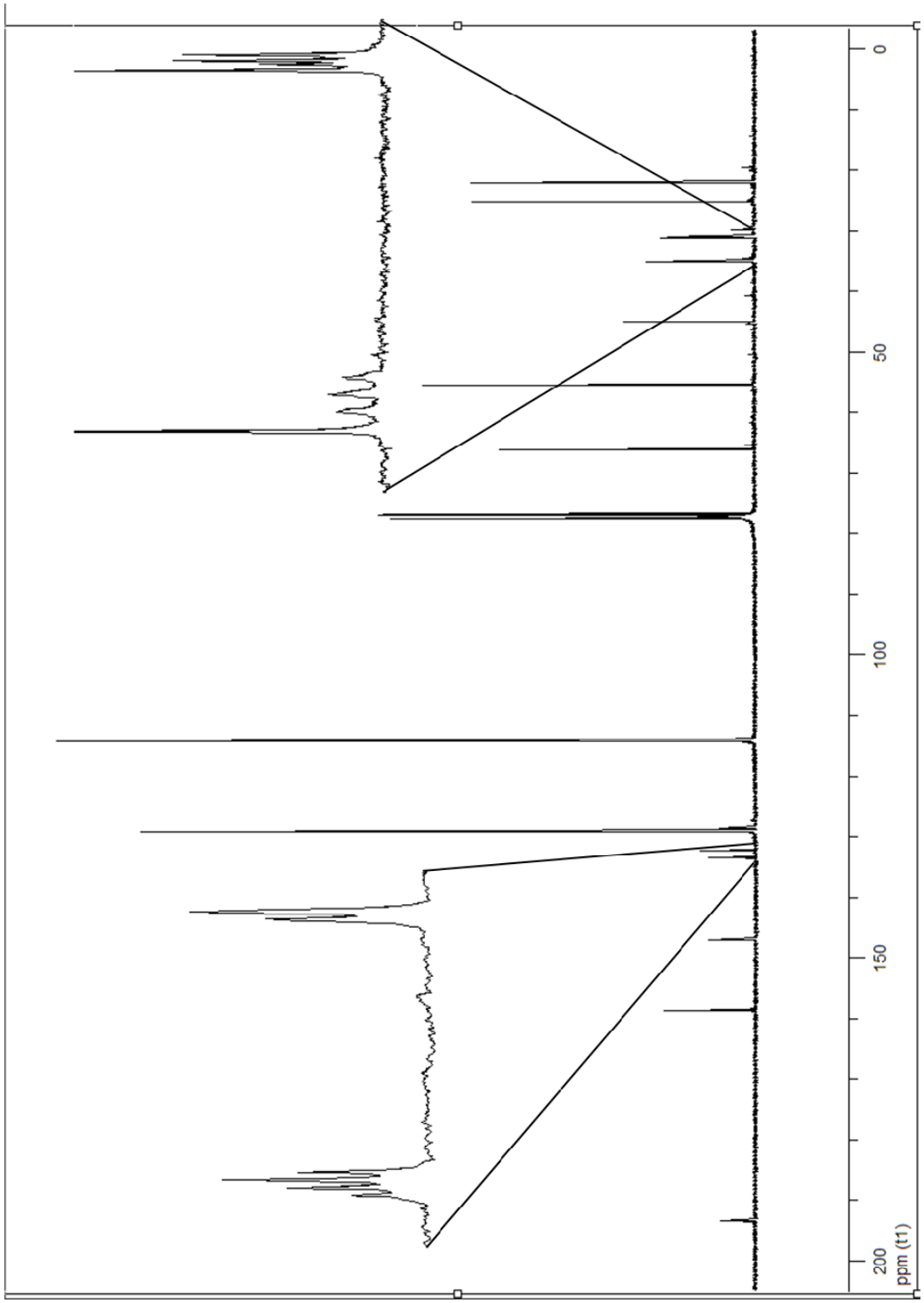
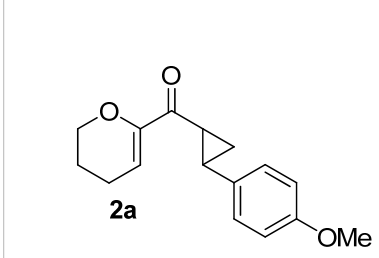
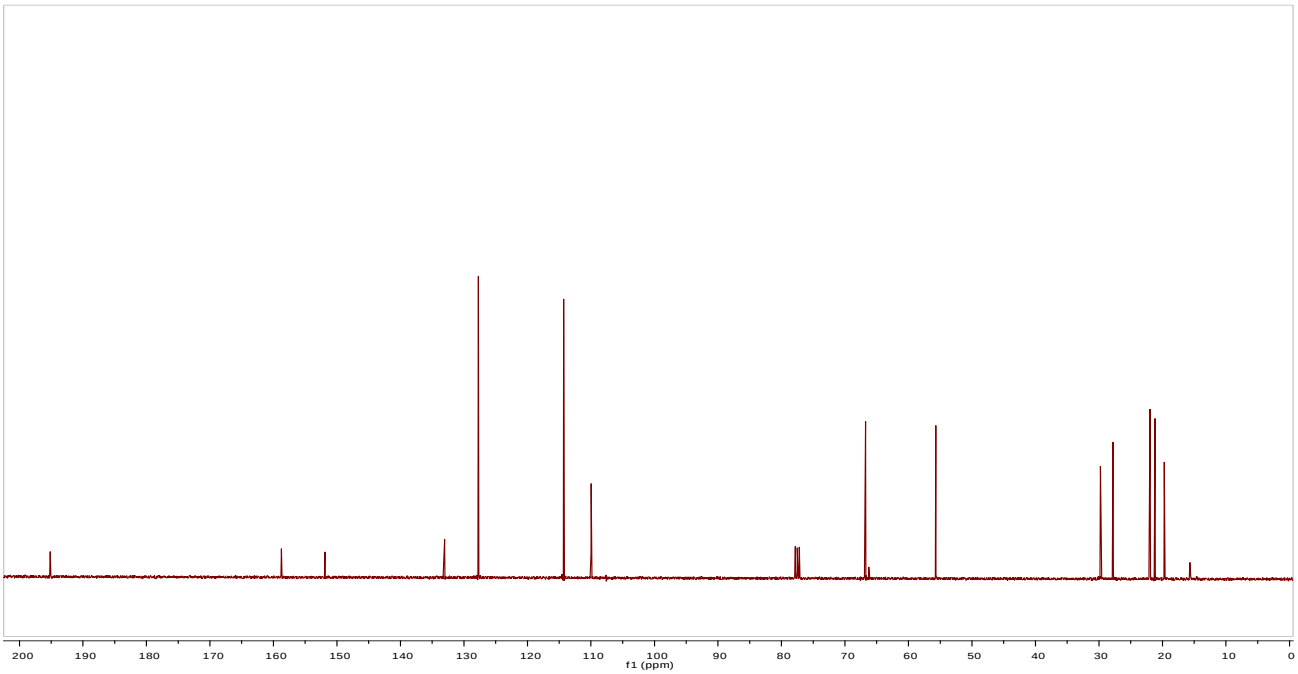


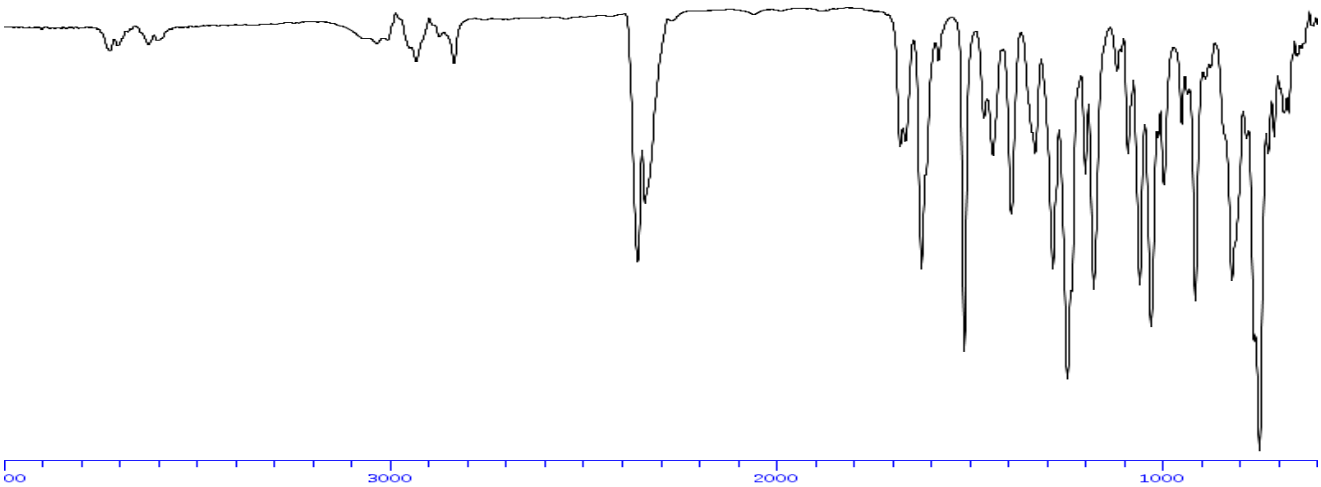
Figure S7 ^{13}C NMR spectra in $CDCl_3$ of cyclization product **3a** obtained using TsOD.

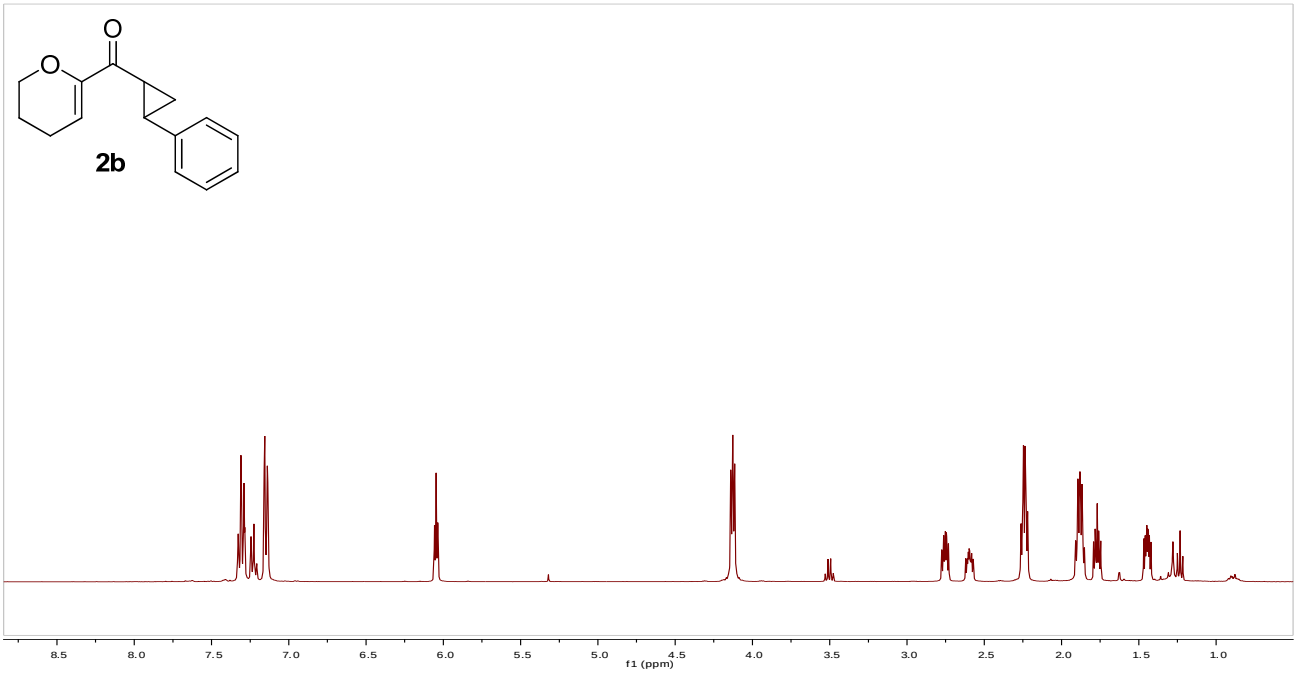
6.2 Spectra of New Compounds



2a



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2b
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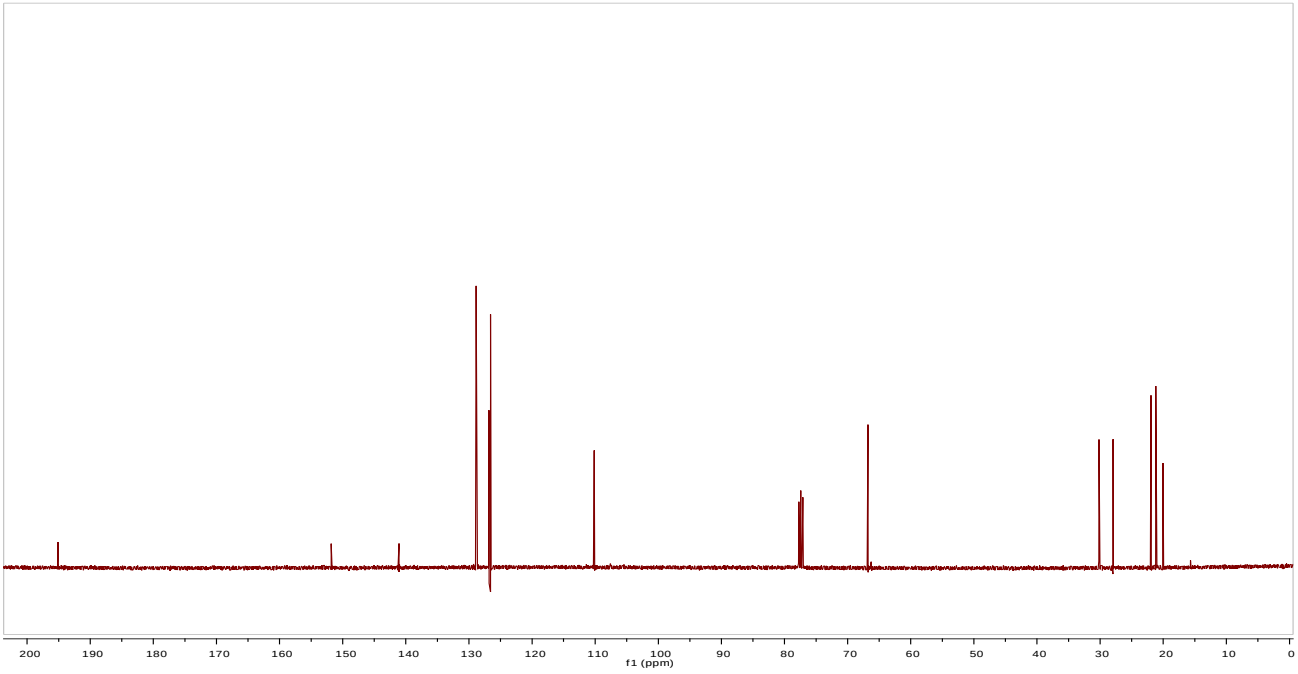
1.0
f1 (ppm)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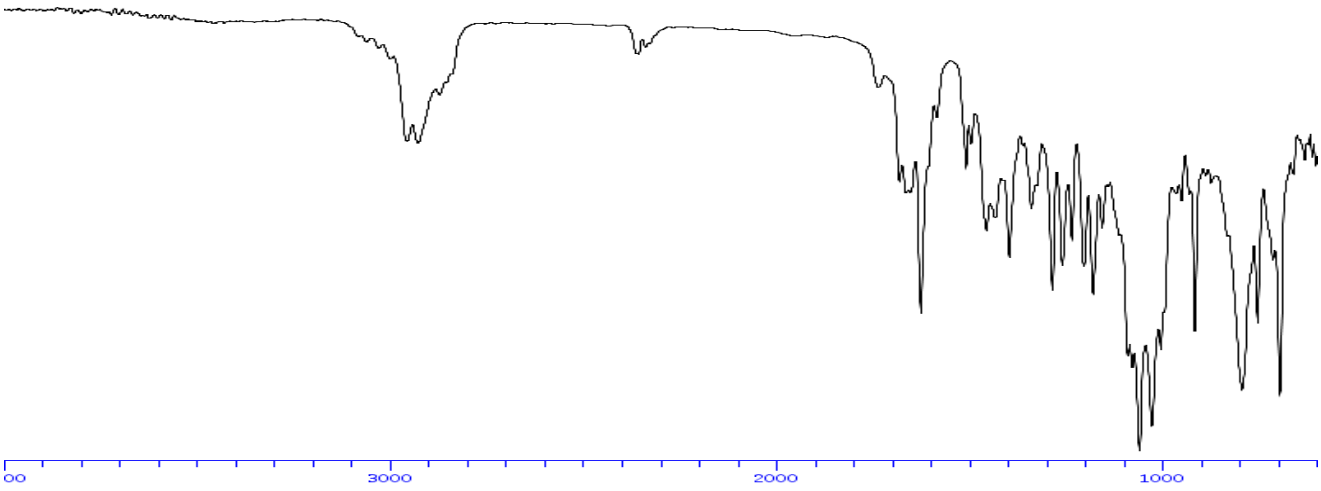
f1 (ppm)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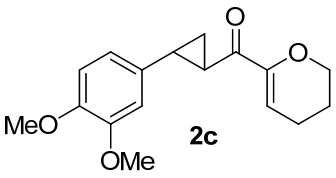
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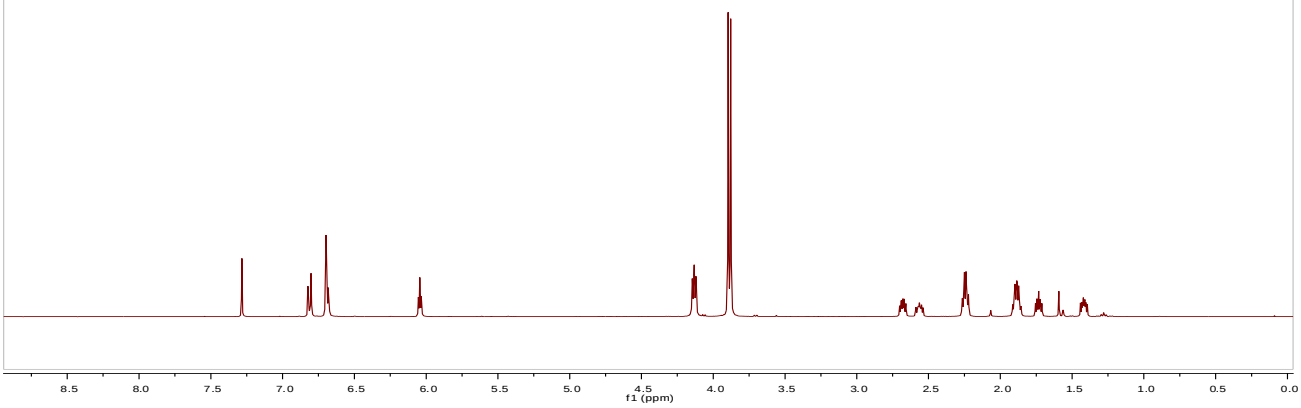
MeO
OMe

2c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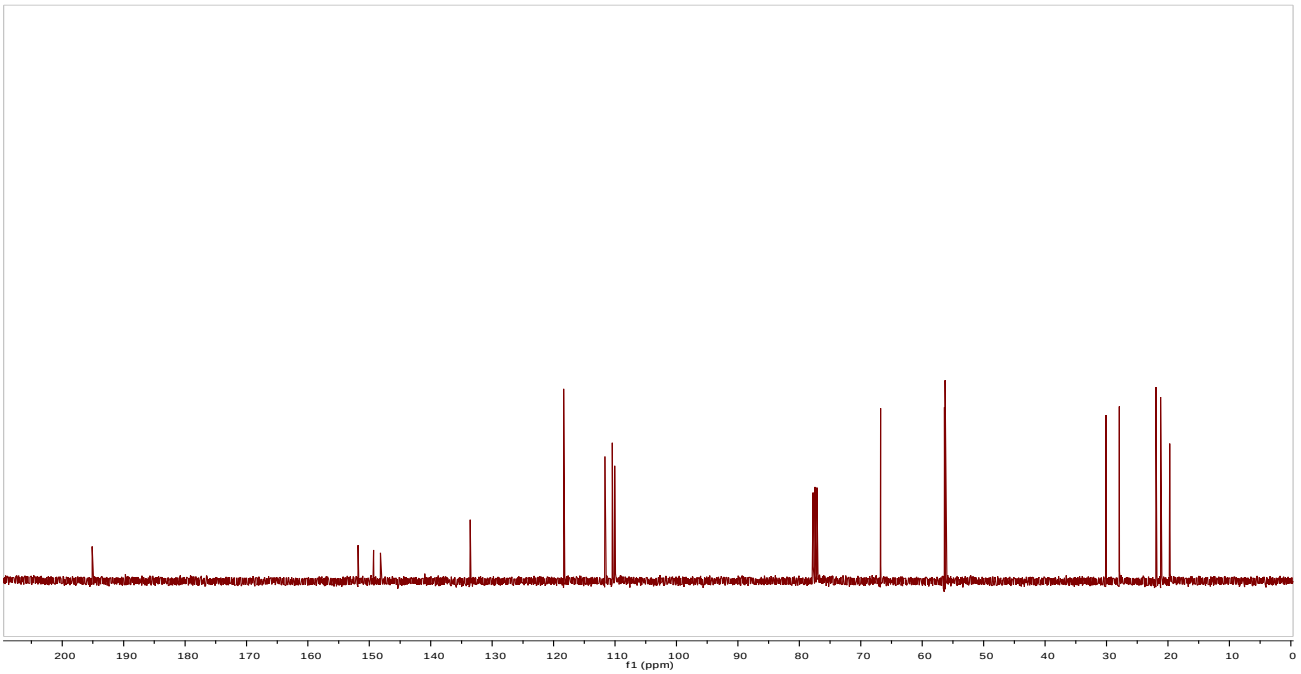
f1 (ppm)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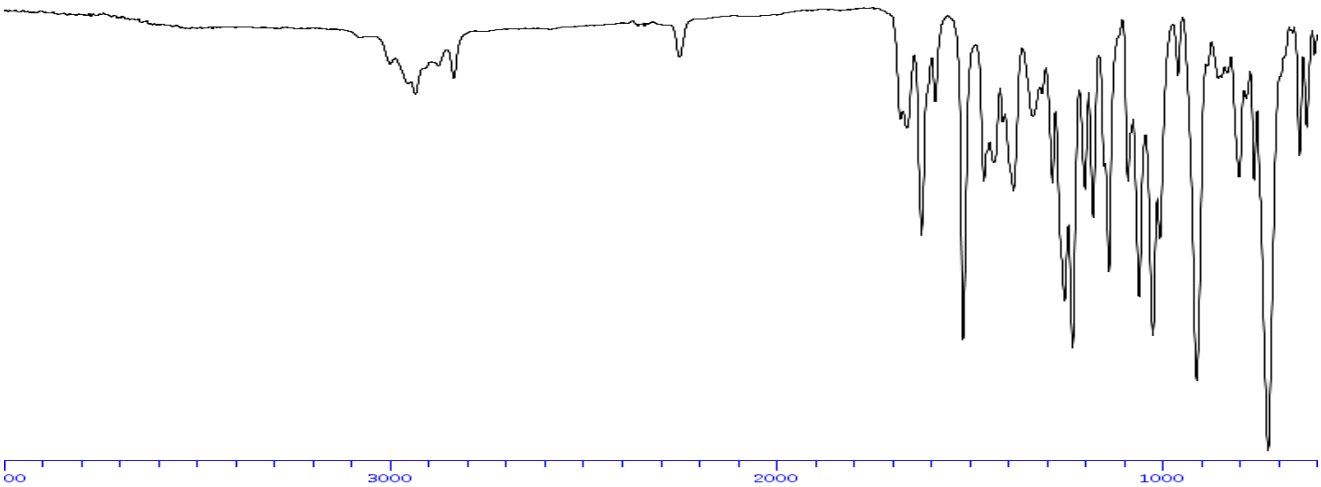
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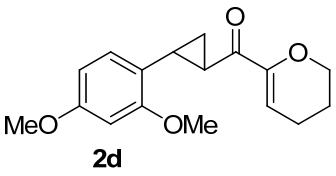
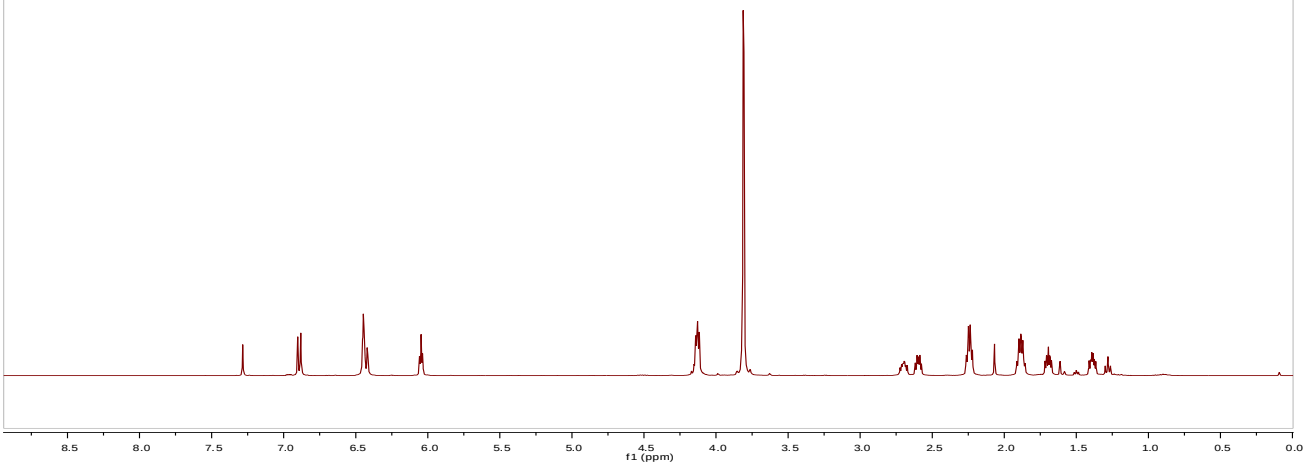

O
O
MeO
OMe

2d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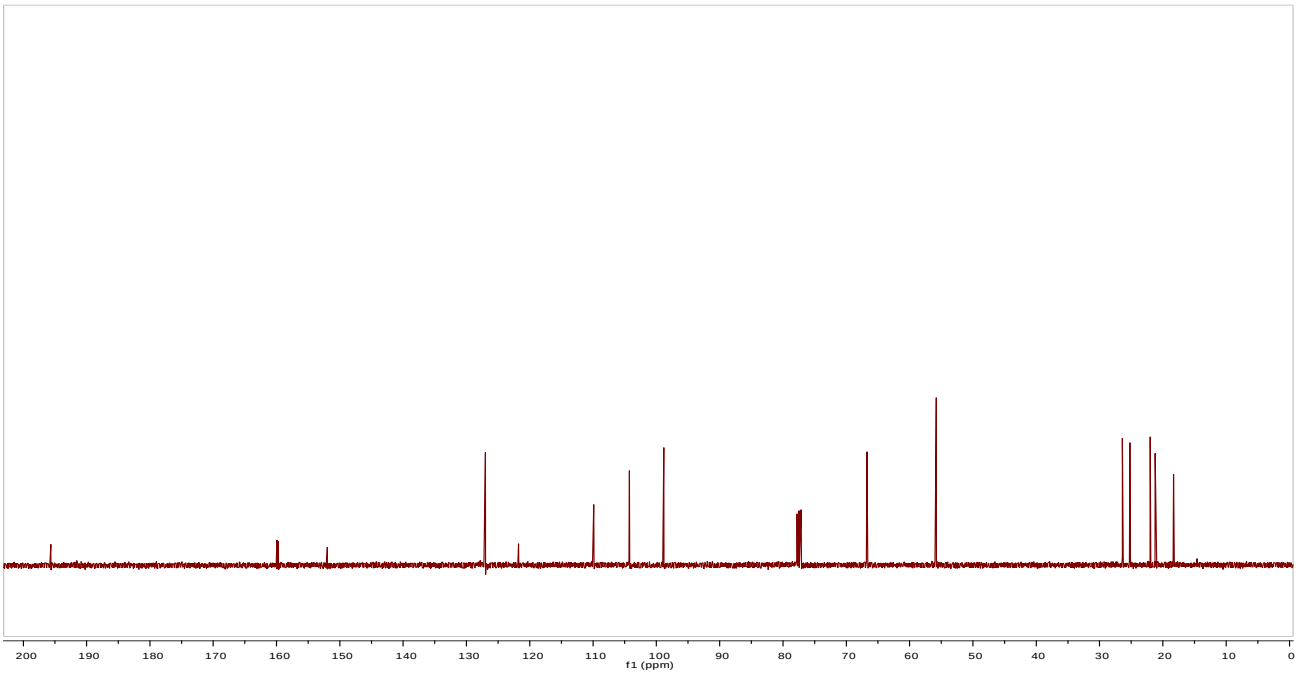
f1 (ppm)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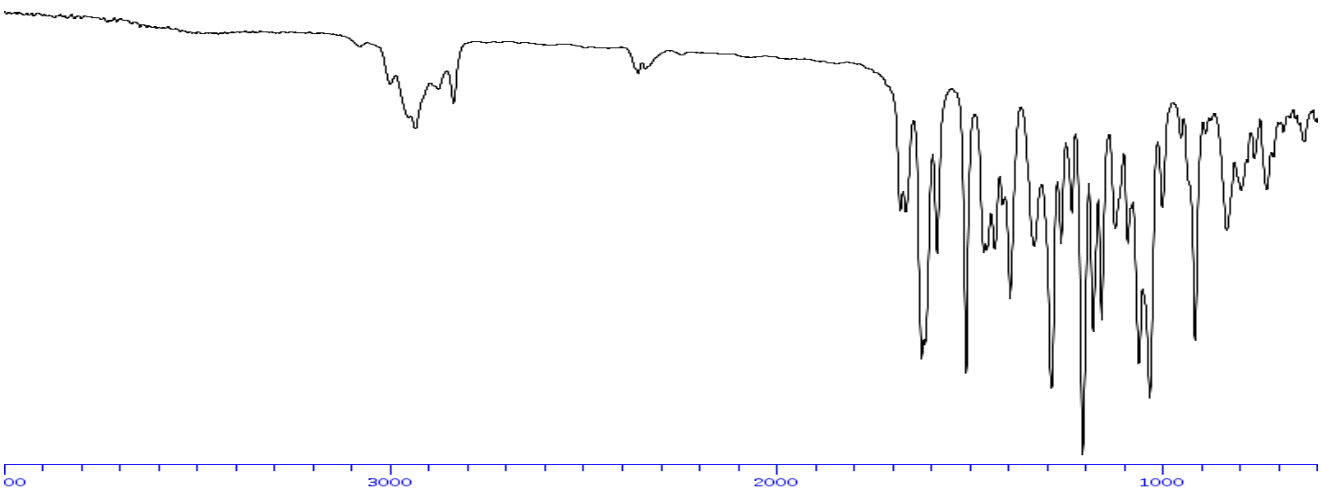
f1 (ppm)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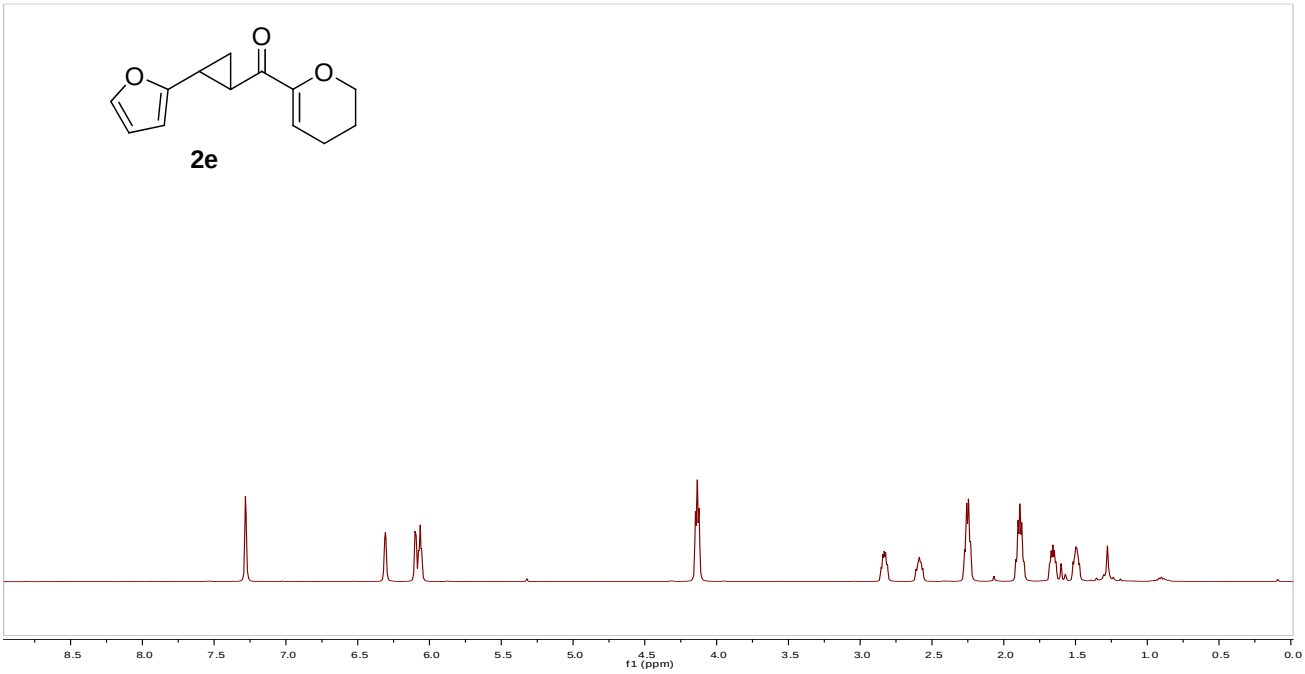
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O
O
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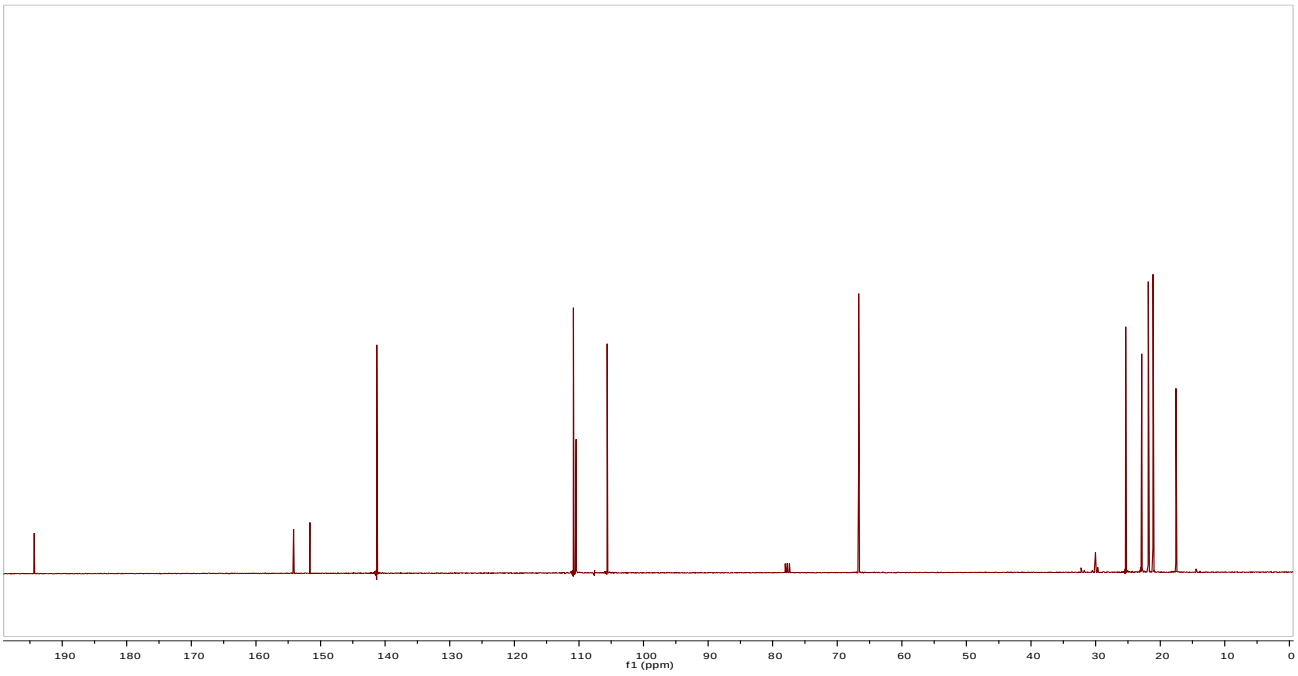
0.0
f1 (ppm)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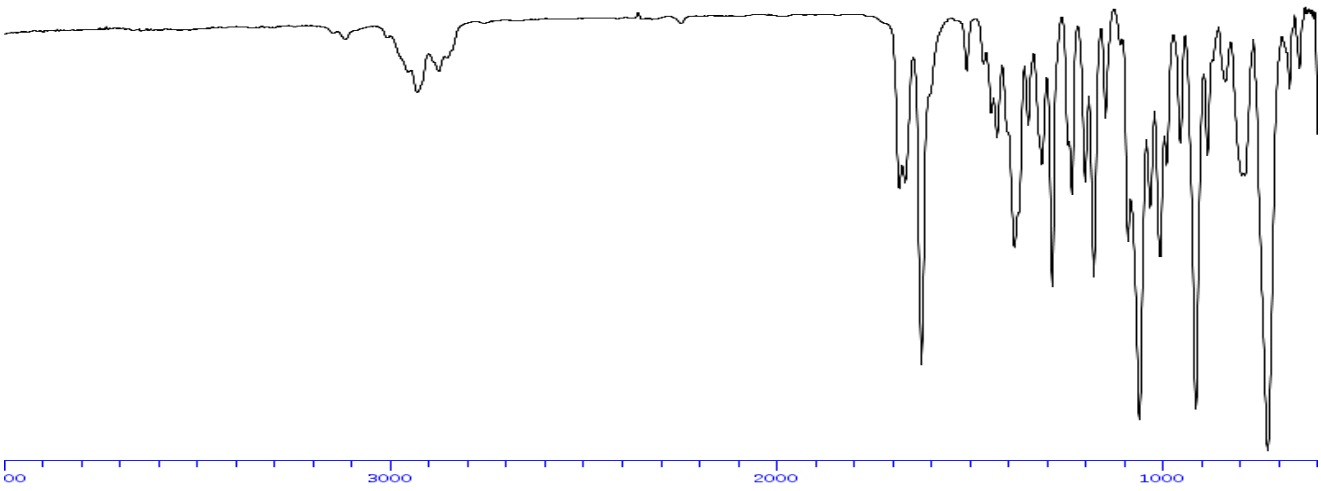
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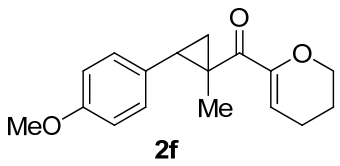
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O
Me
MeO

2f

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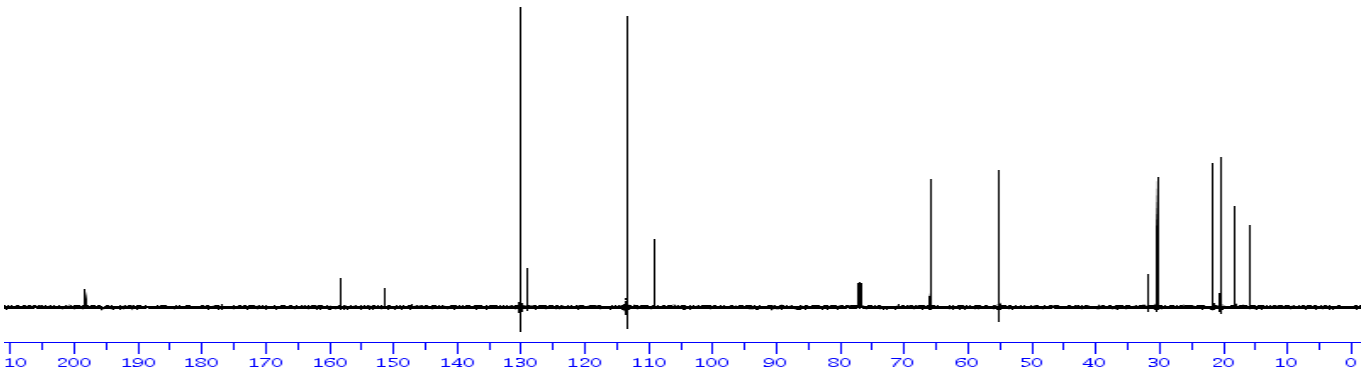
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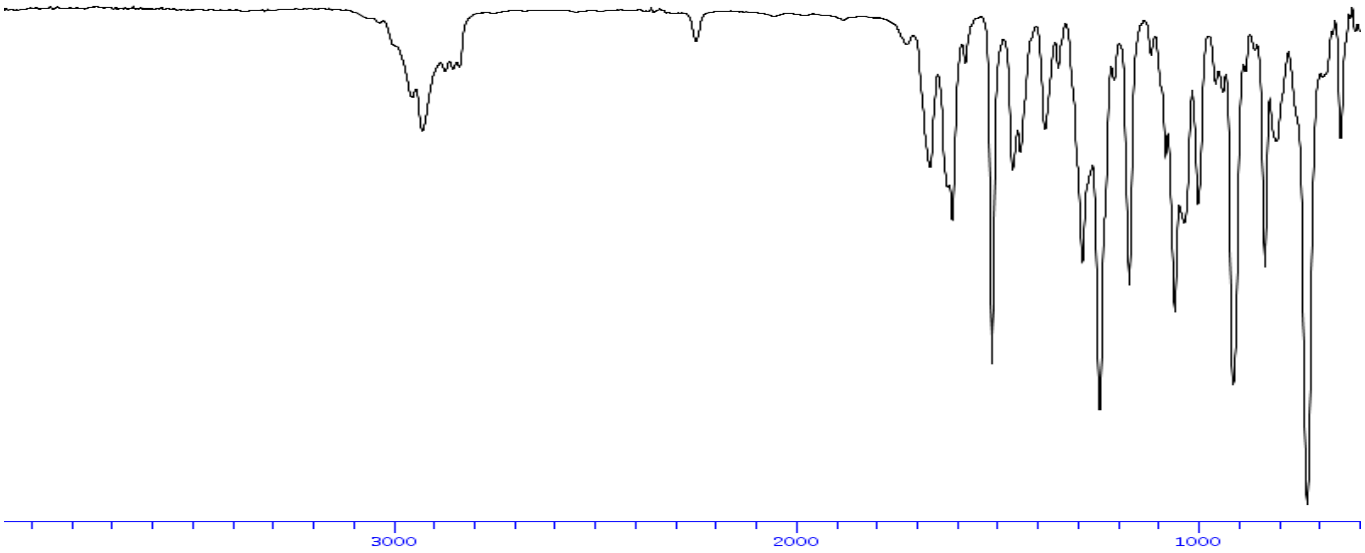
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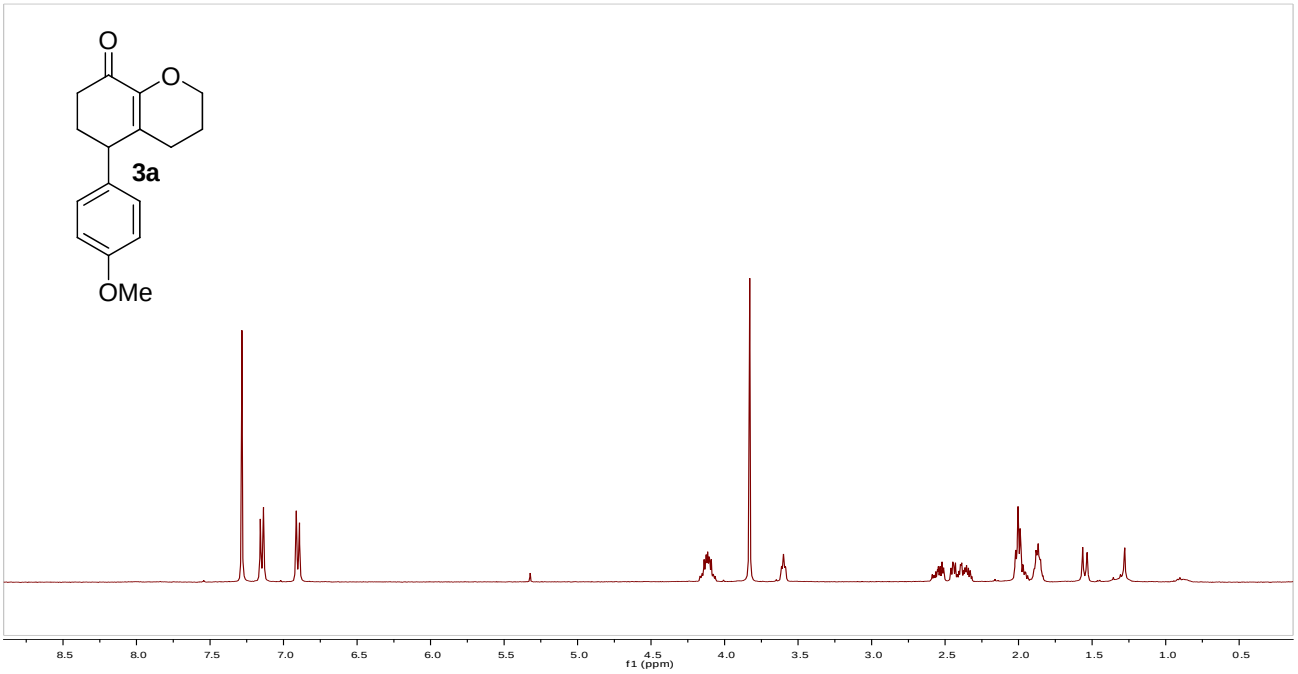
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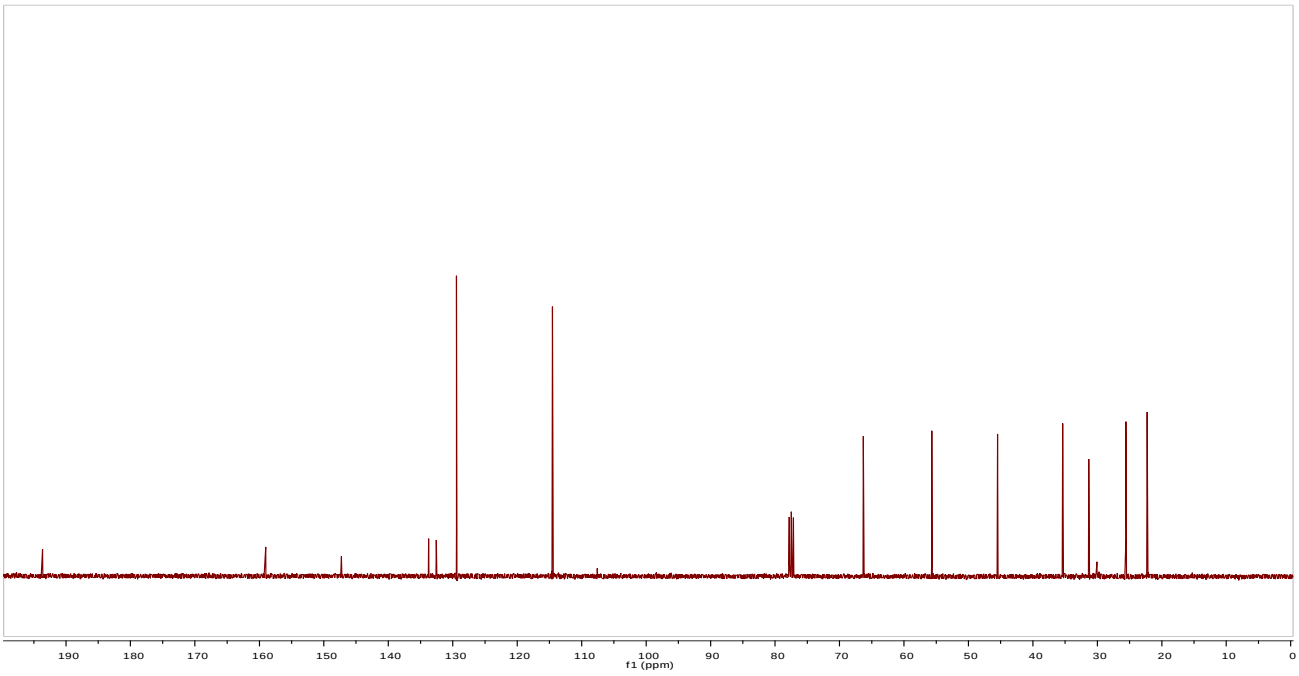
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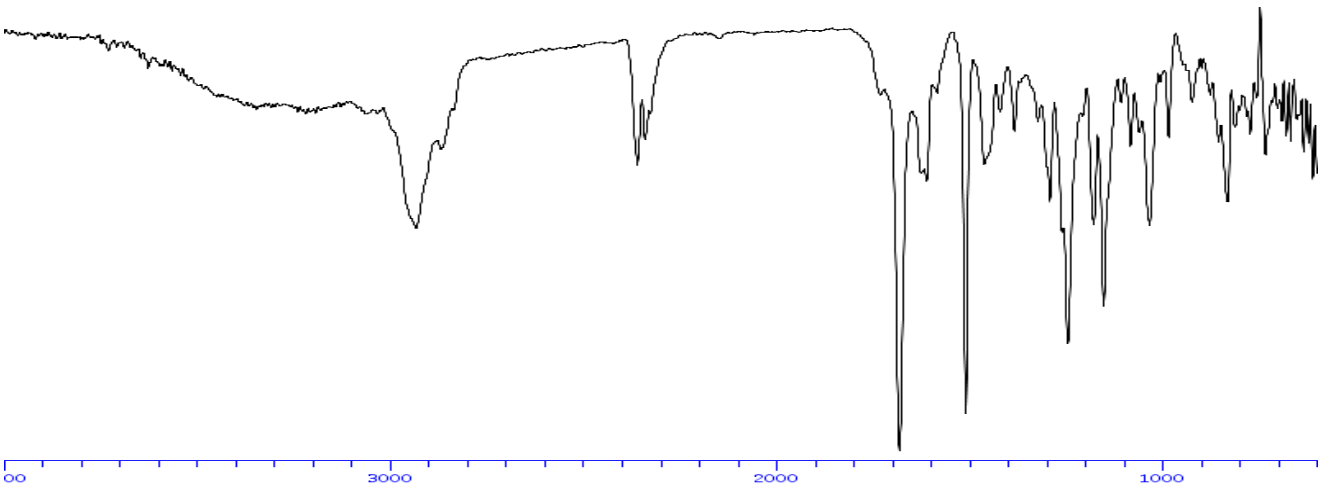
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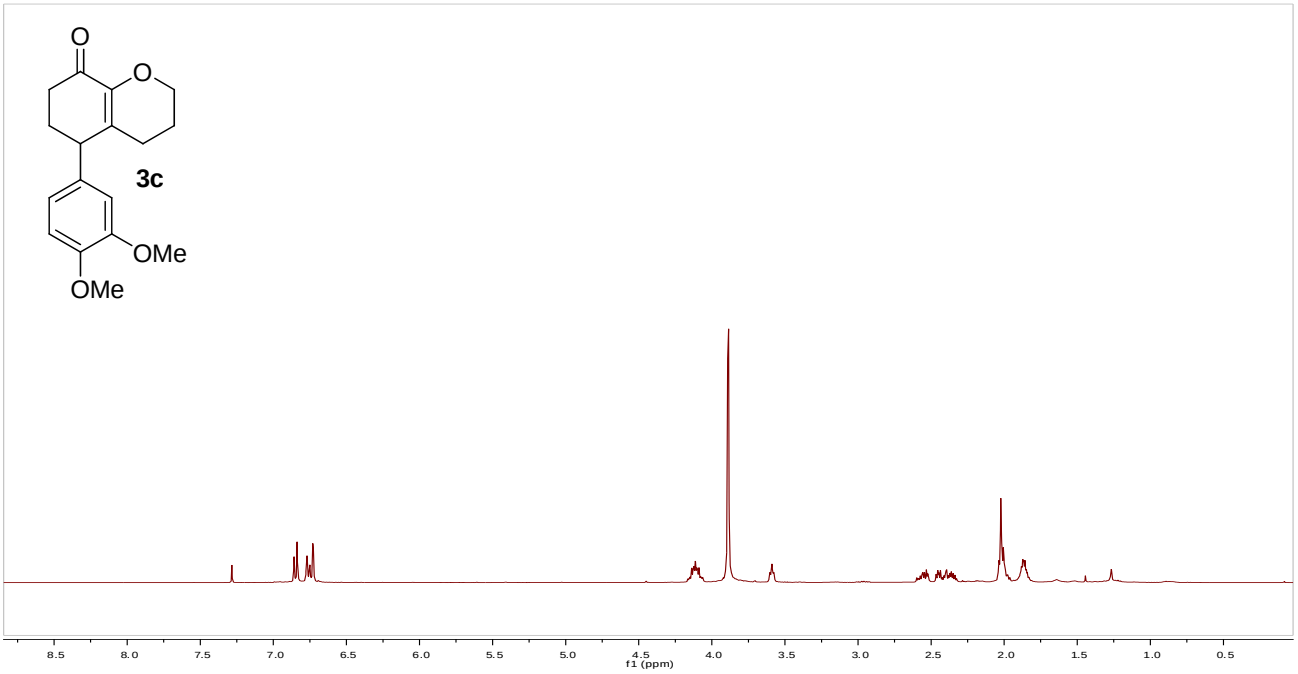
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3c
OMe
OMe
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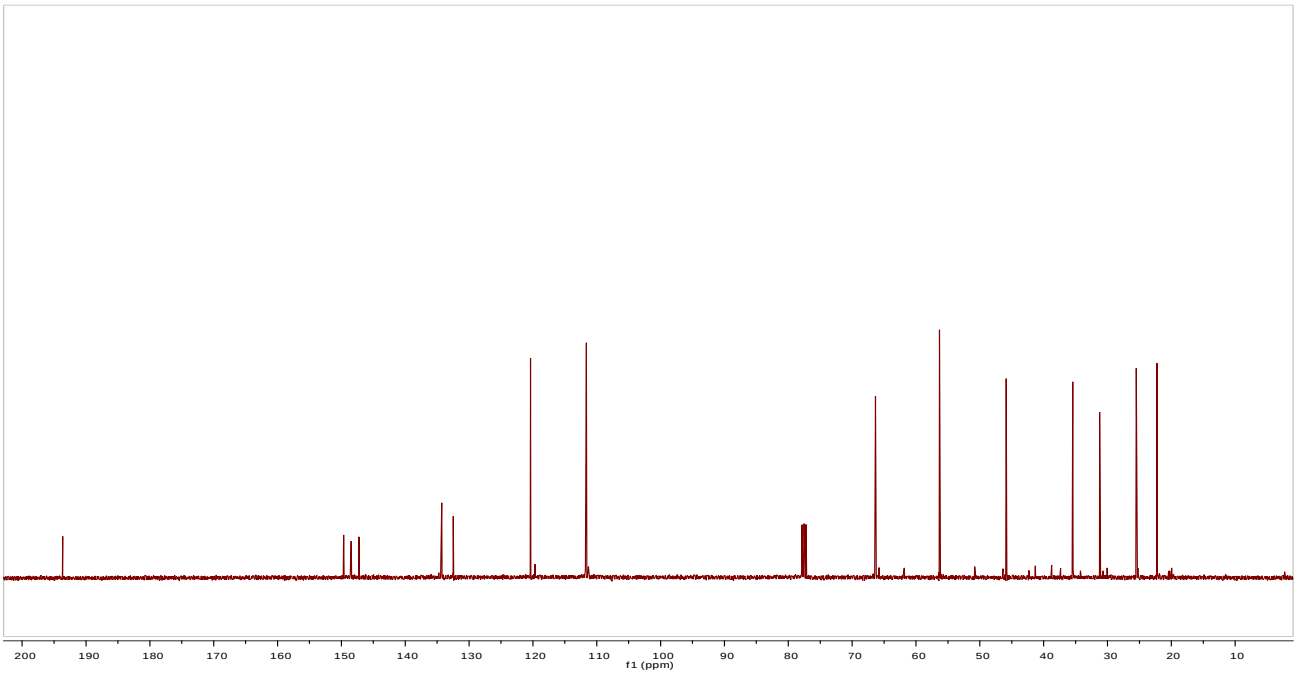
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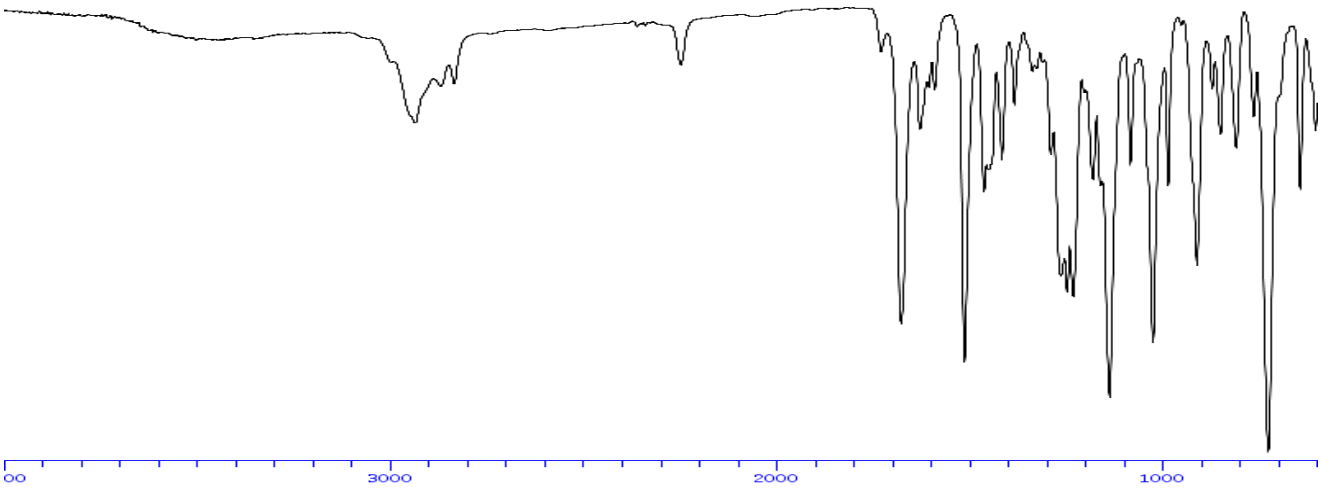
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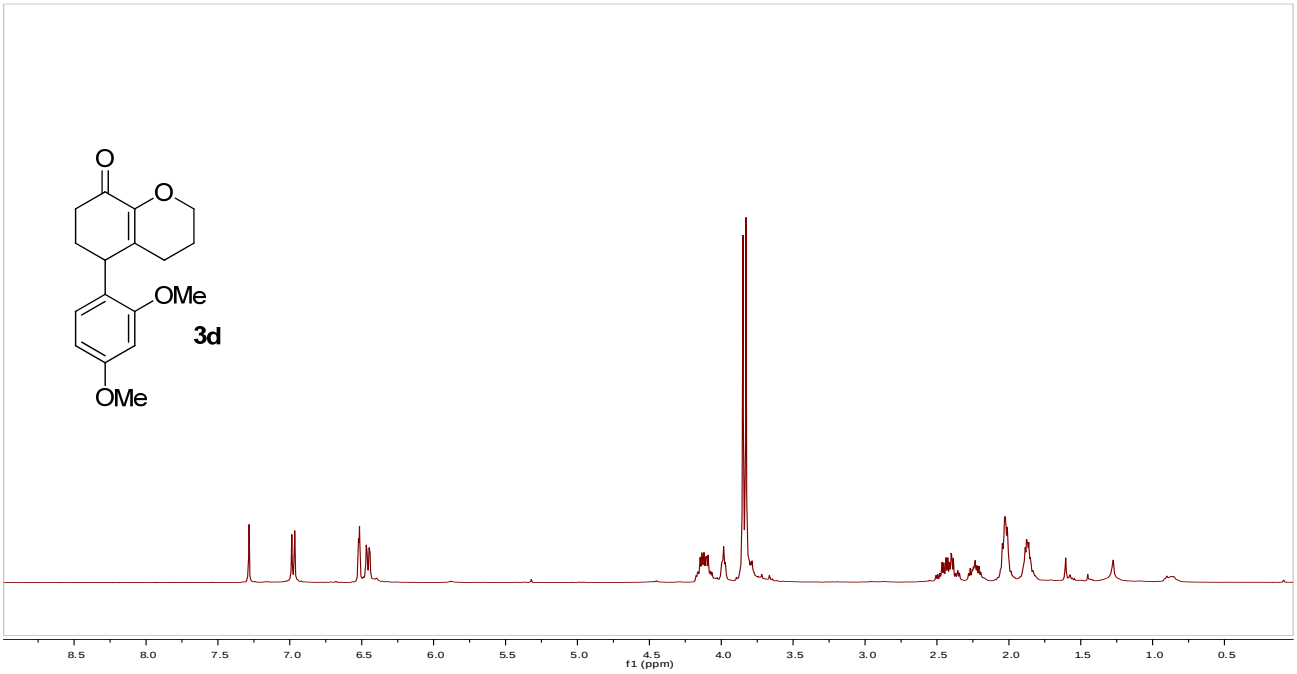
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OMe
OMe
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4.0
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3.0
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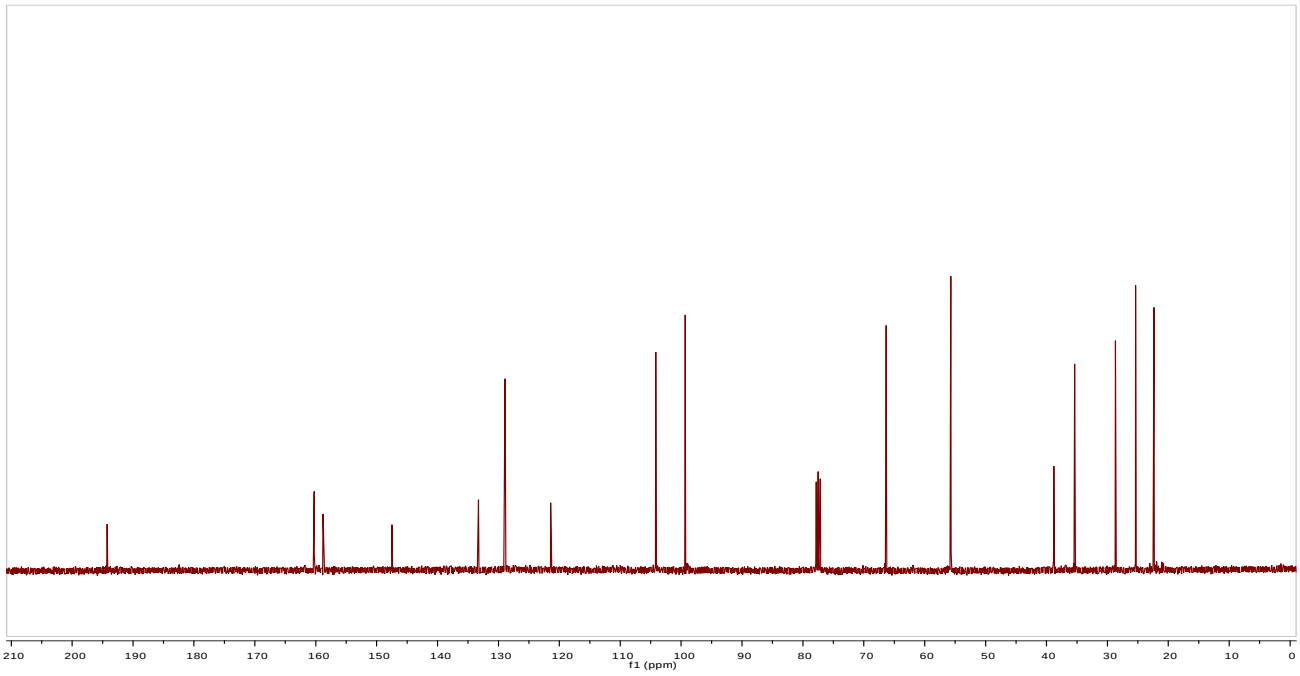
1.0
0.5
f1 (ppm)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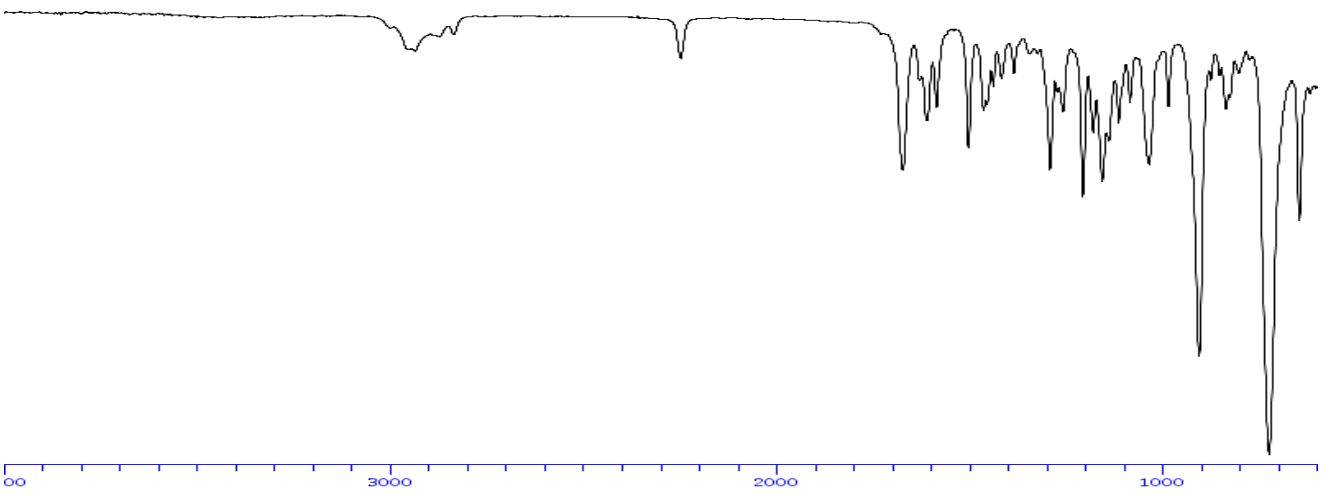
f1 (ppm)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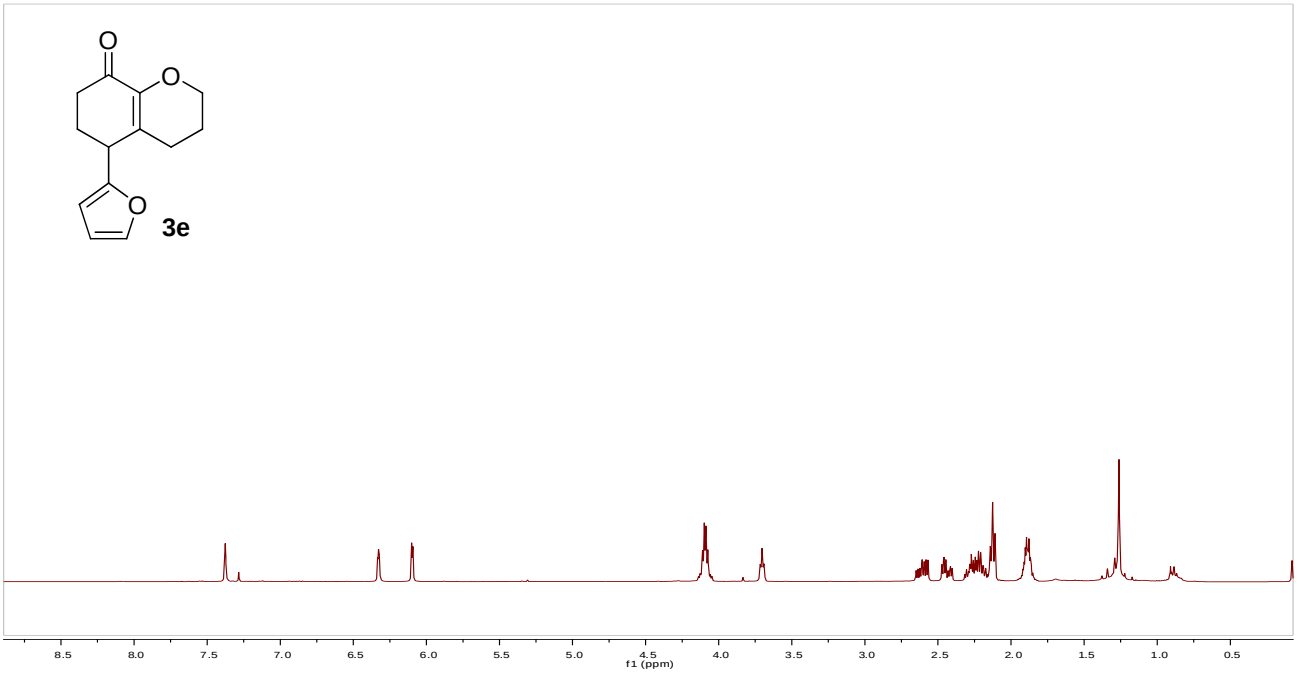
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3.0
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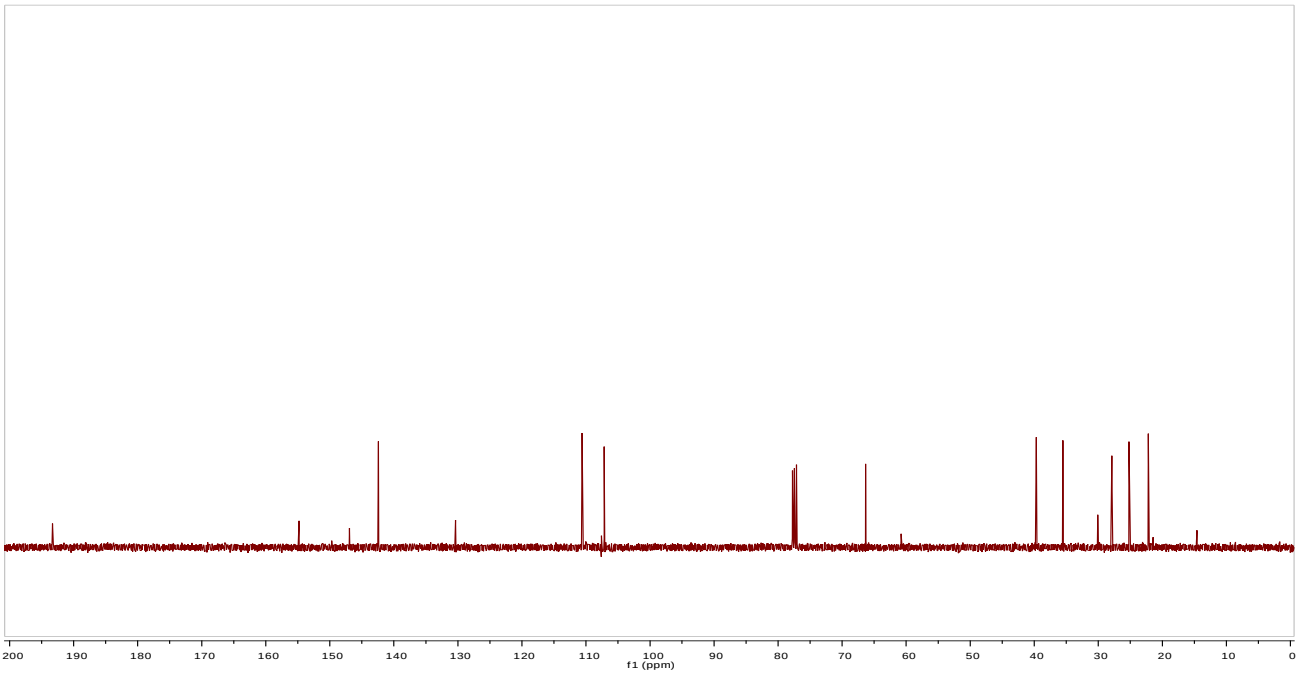
1.5
1.0
0.5
f1 (ppm)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100
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80
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50
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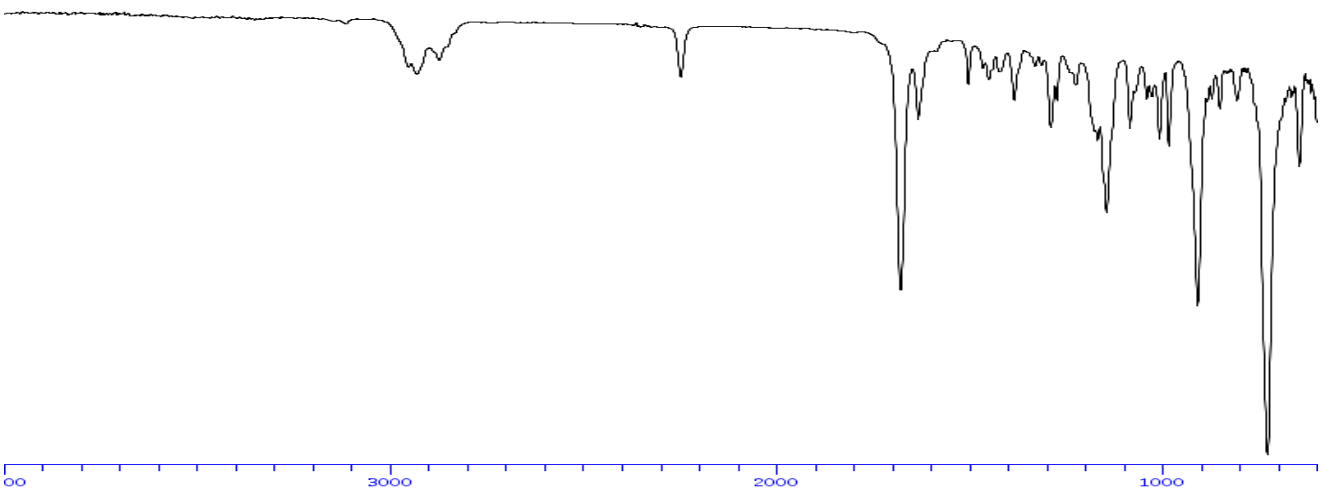
f1 (ppm)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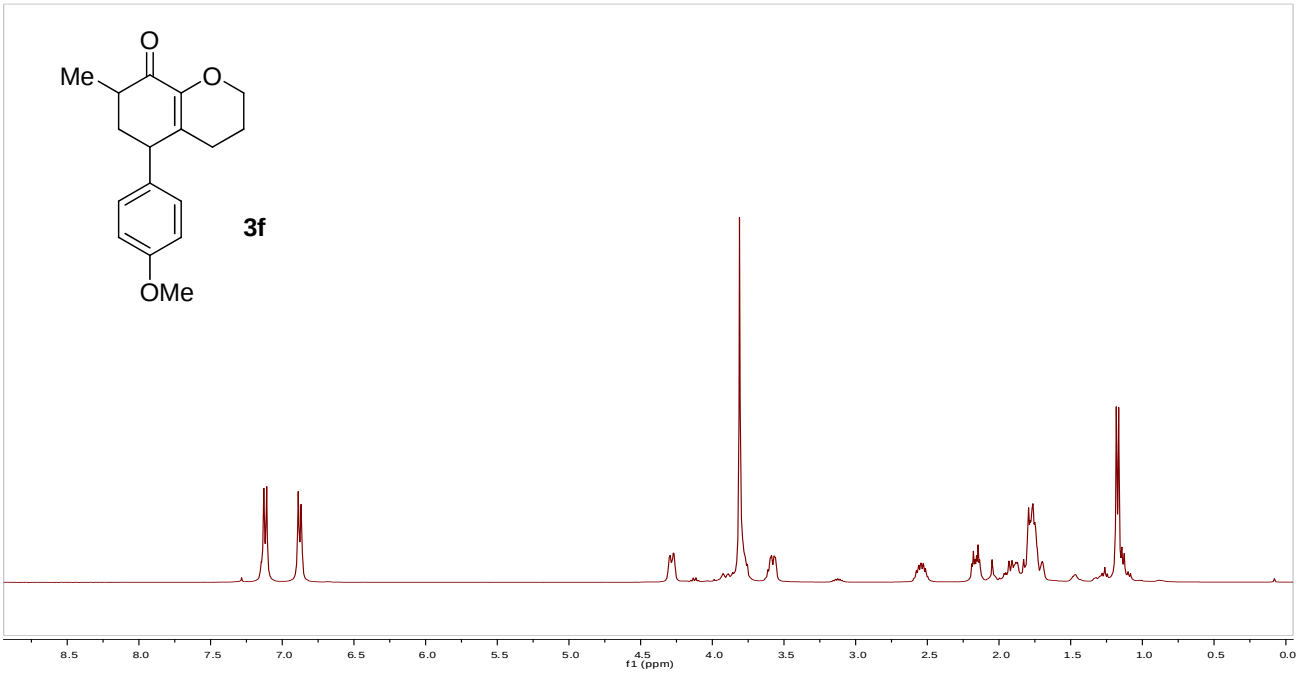
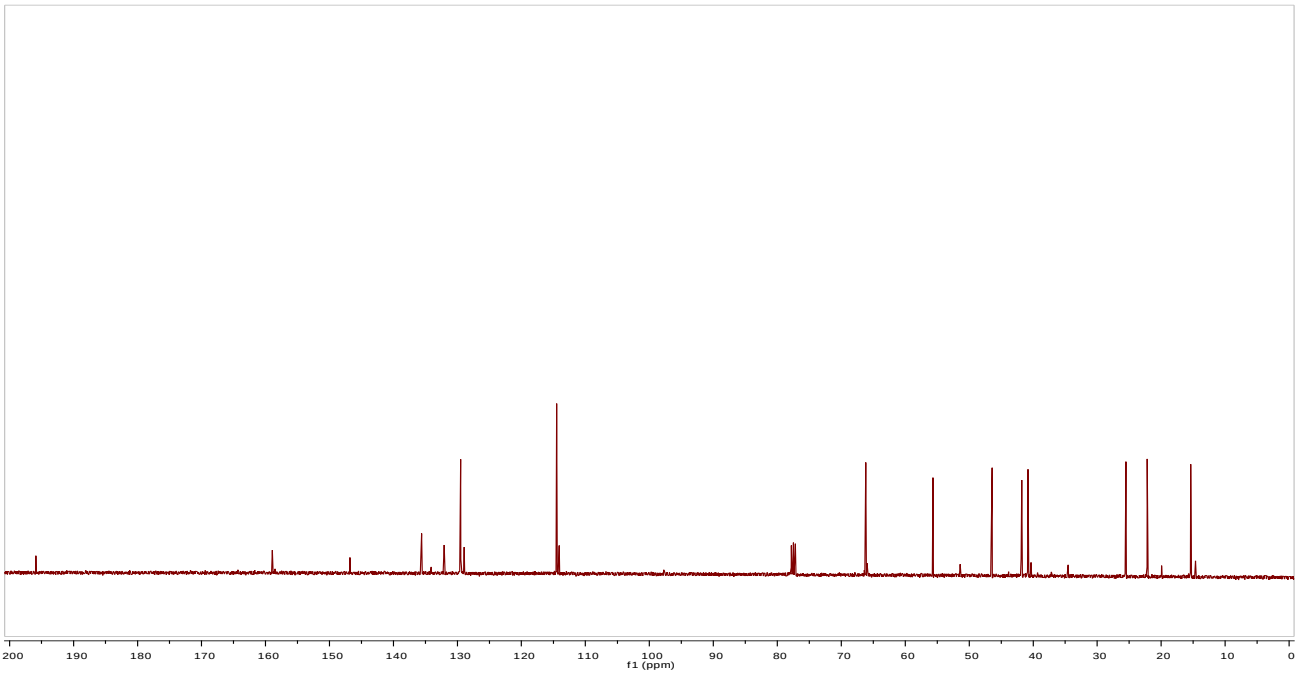
1000


O
Me
O
OMe
3f
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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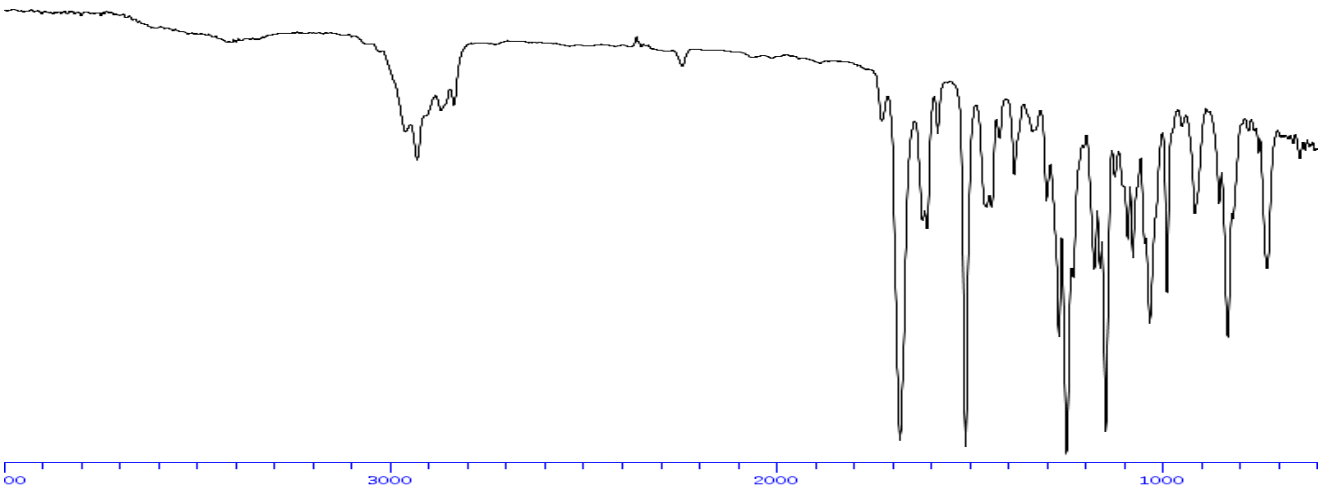
f1 (ppm)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2000
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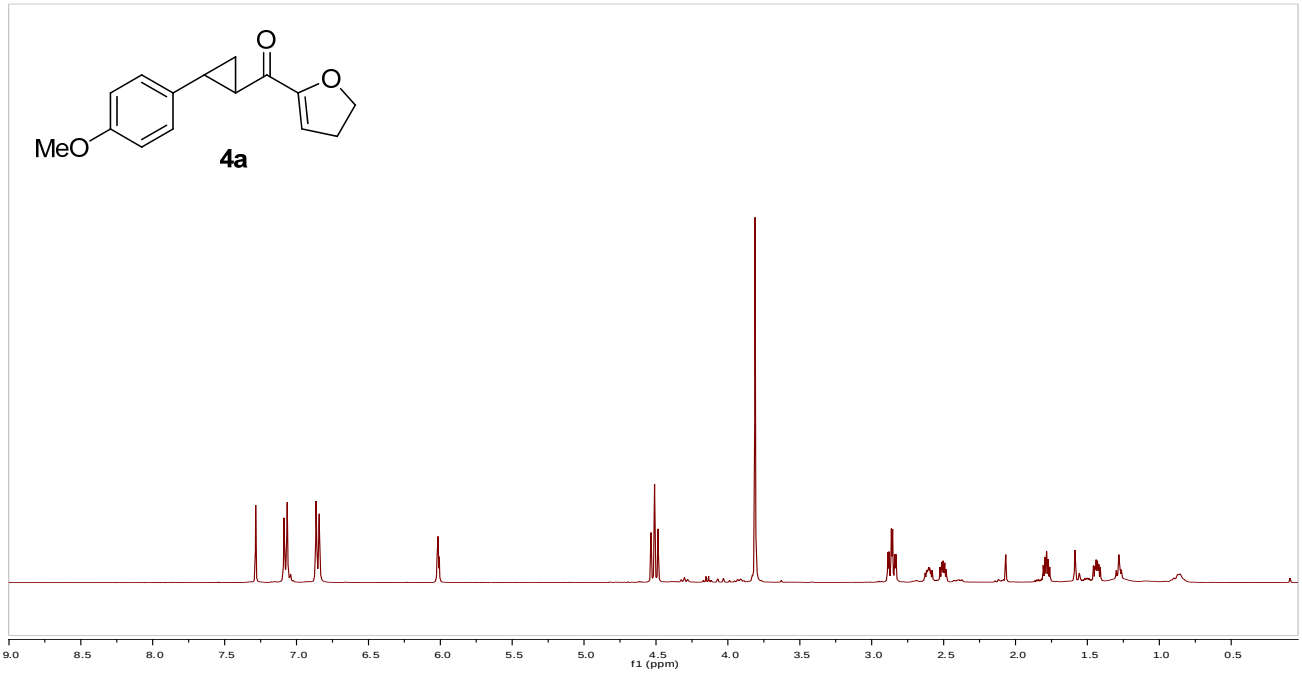
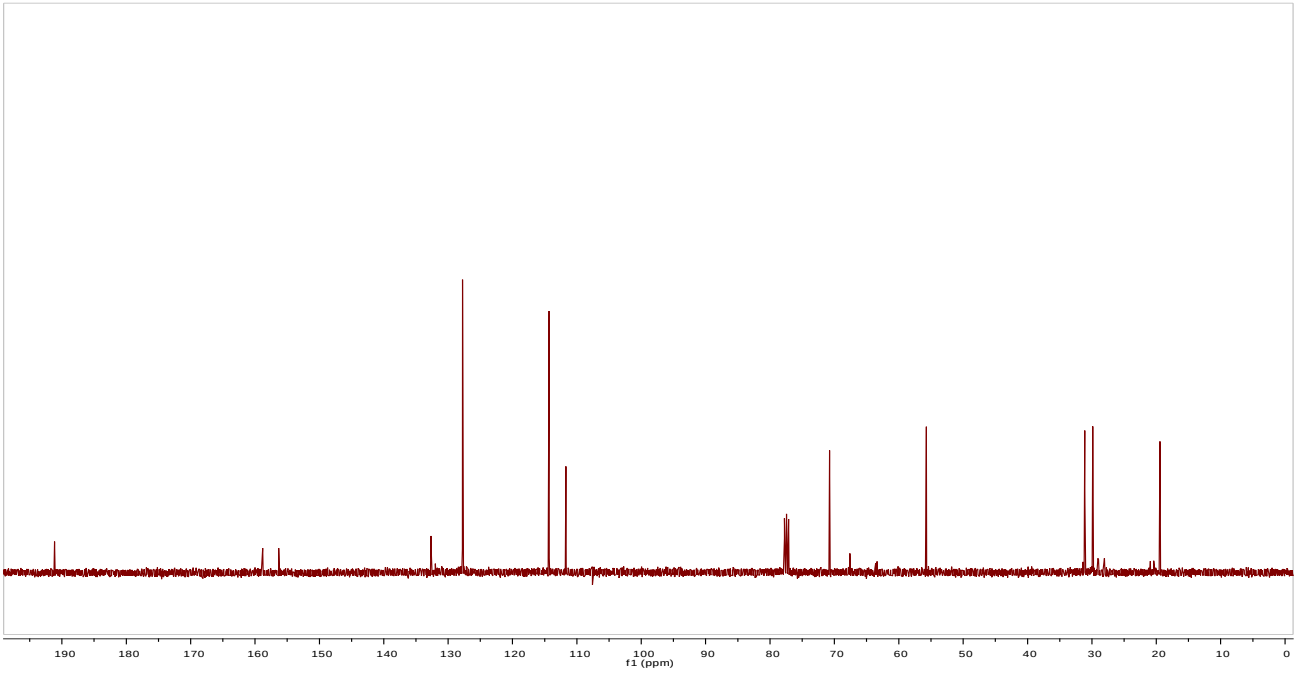

O
O
MeO
4a
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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180
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160
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110
100
90
80
70
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50
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30
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10
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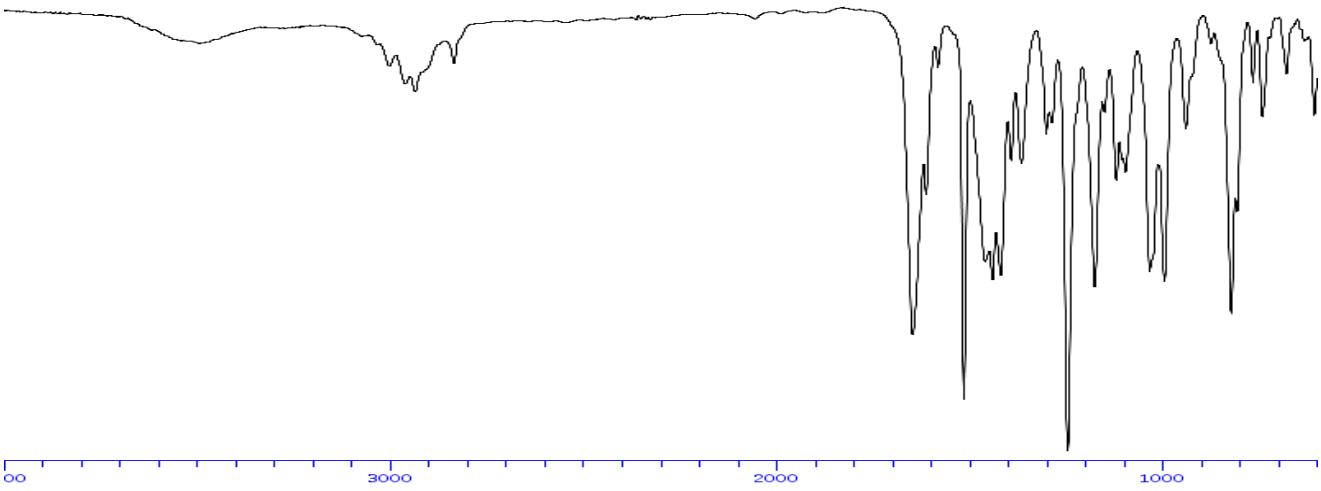
f1 (ppm)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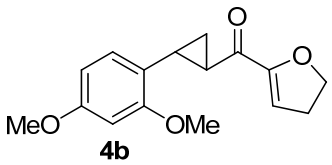
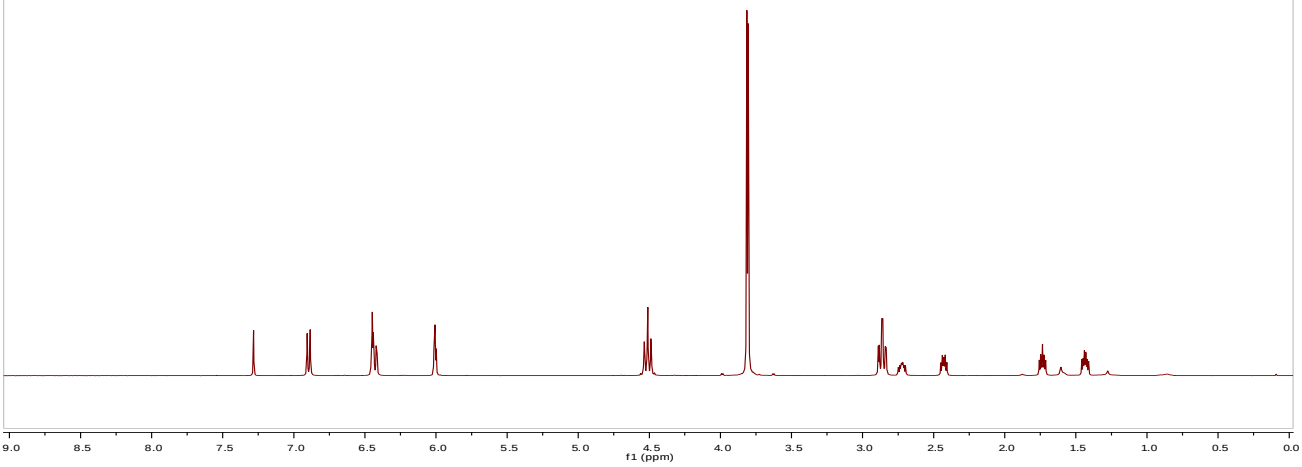

O
O
MeO
OMe

4b


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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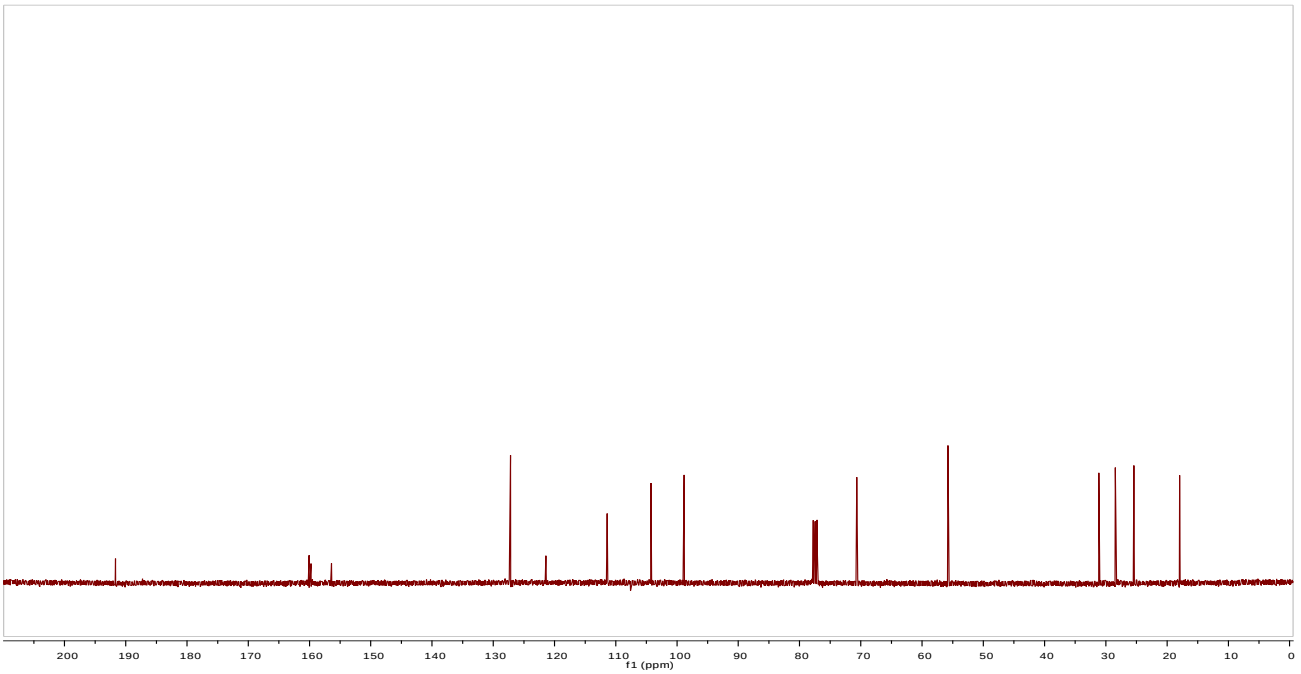
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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100
90
80
70
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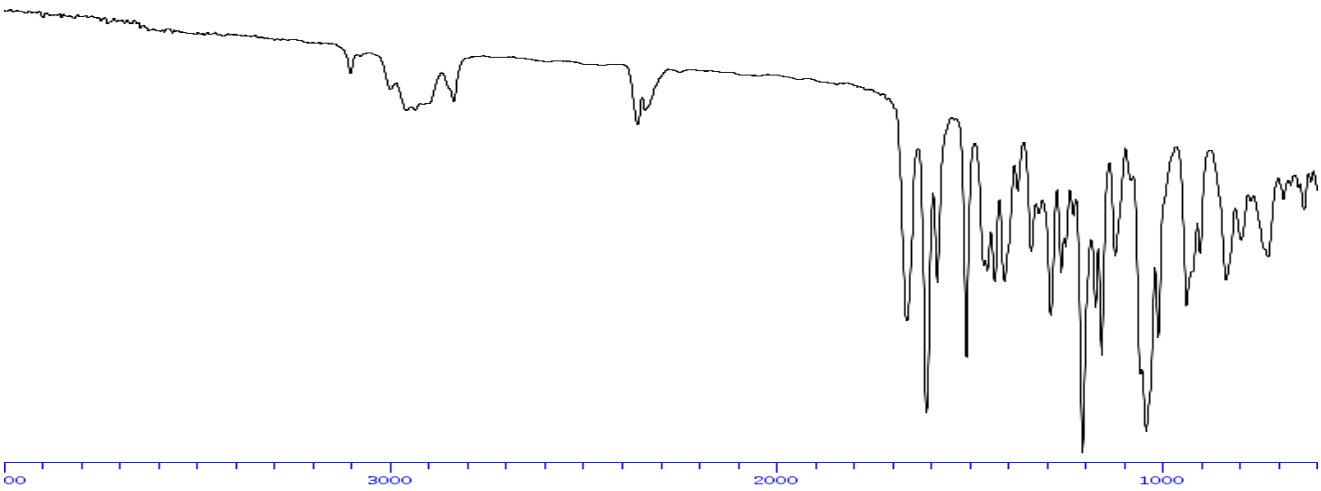
50
40
30
20
10
0
f1 (ppm)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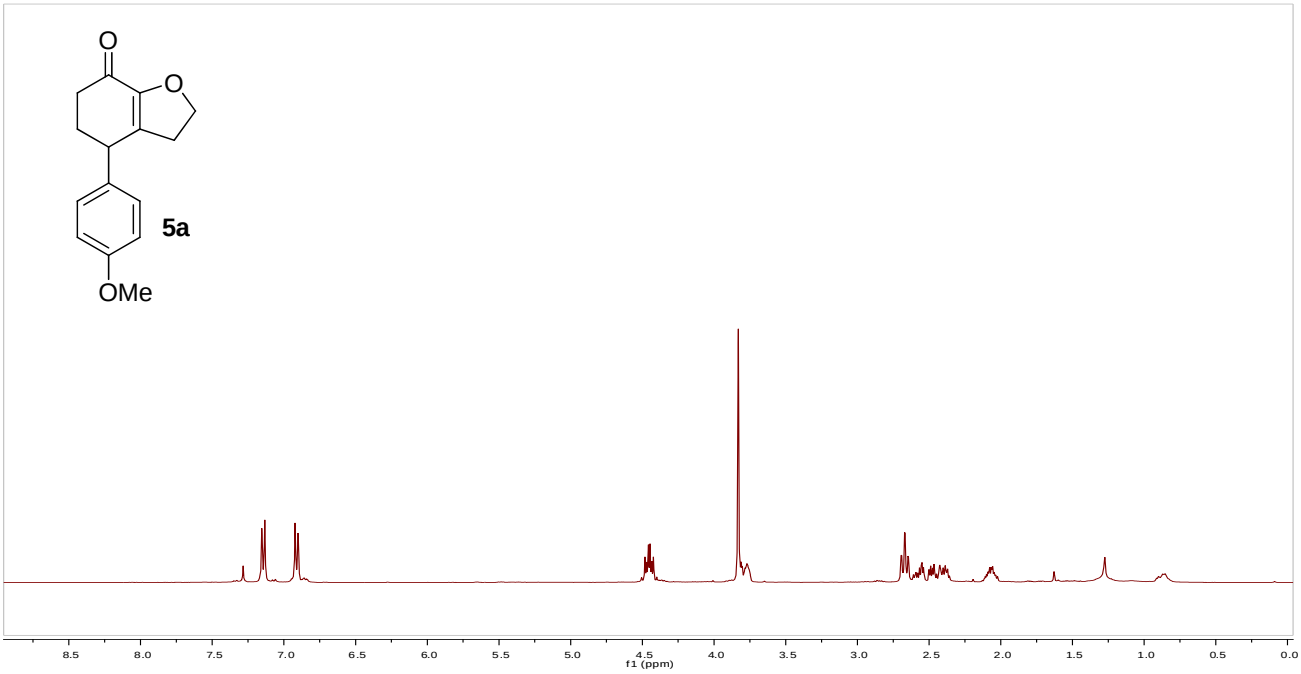
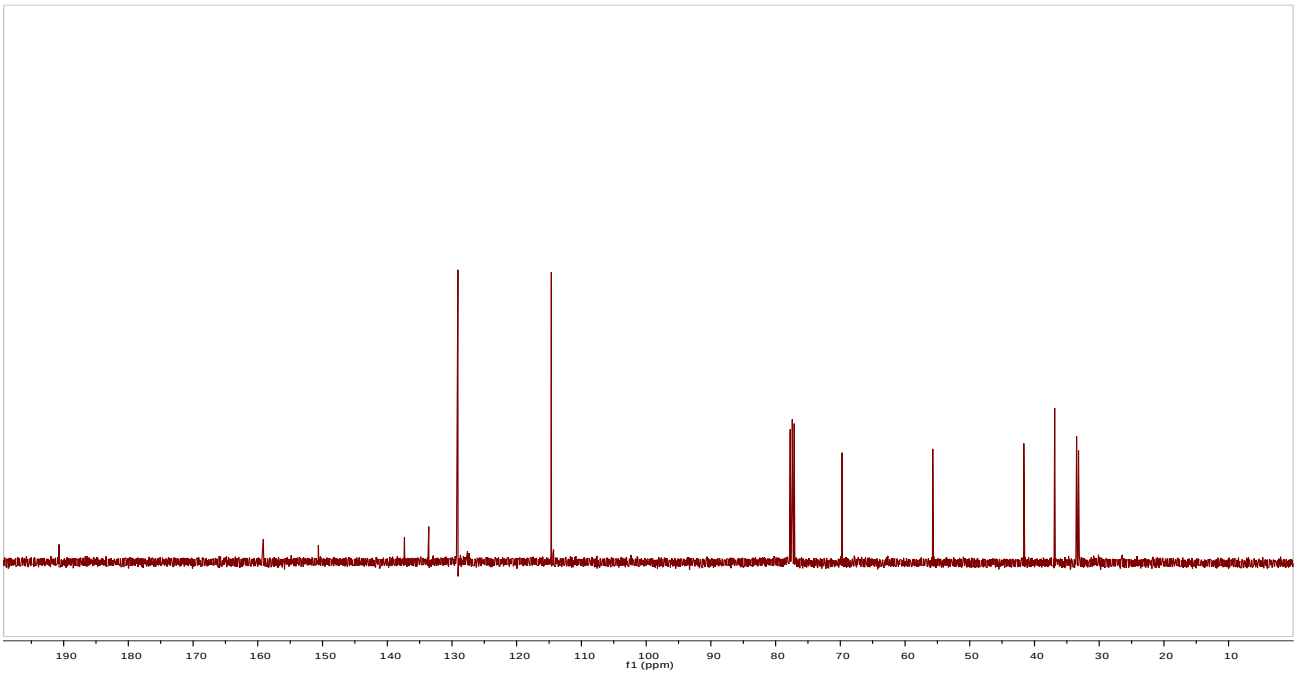
3000
2000
1000


O
O
OMe
5a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


190
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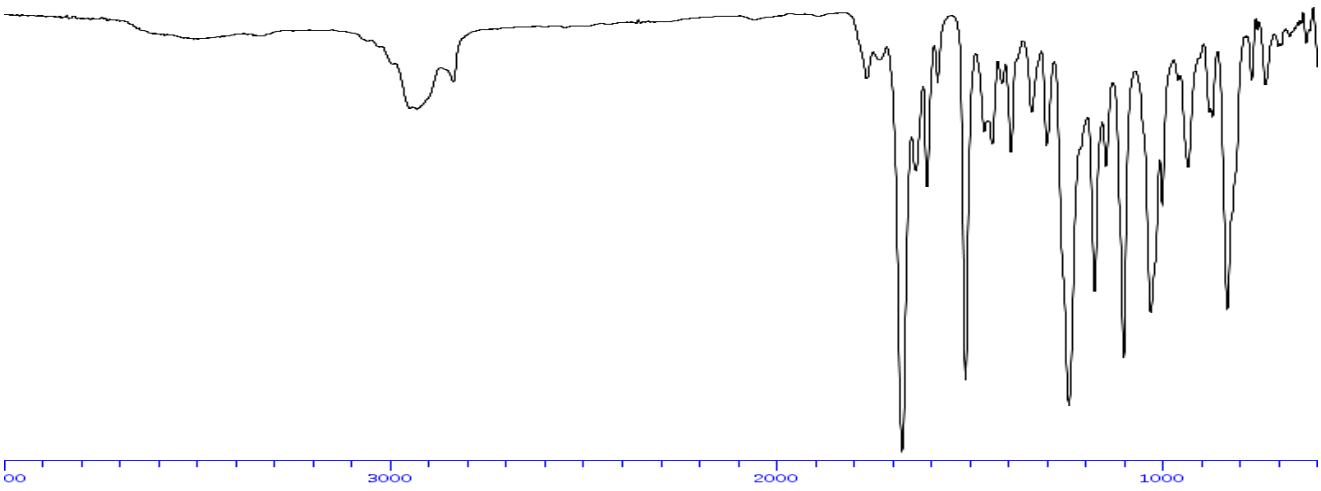
50
40
30
20
10
f1 (ppm)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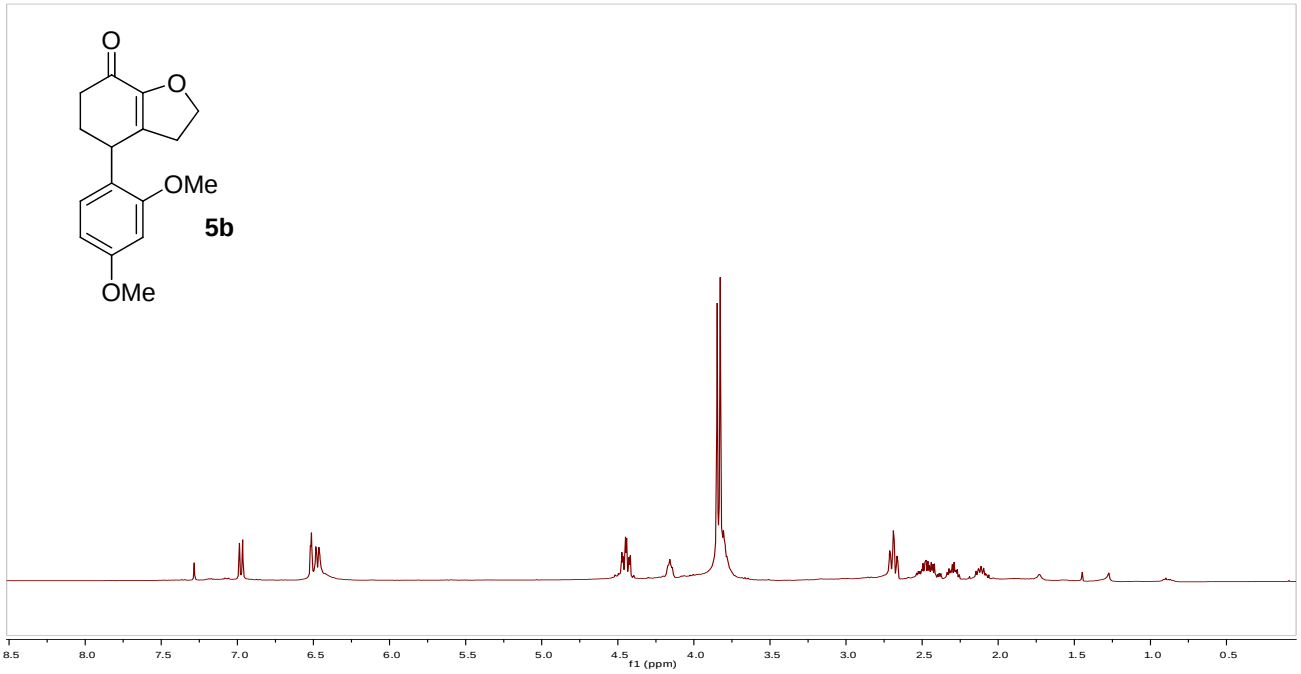
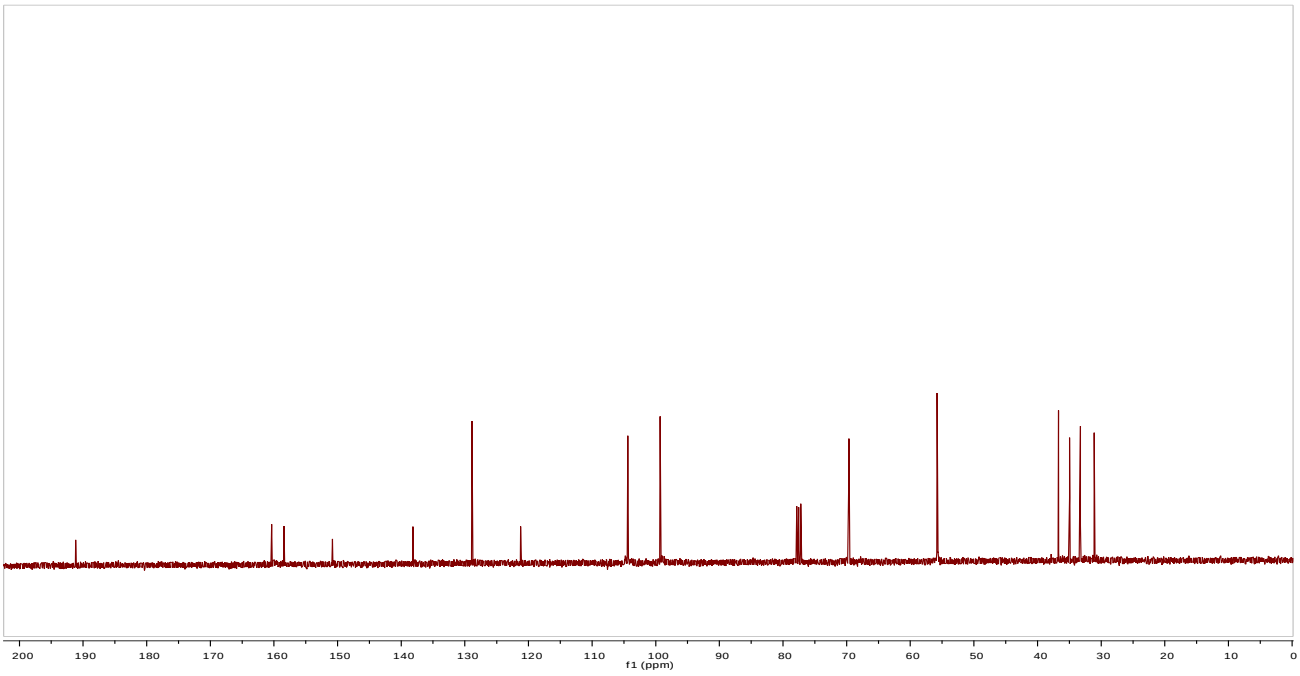

O
O
OMe
OMe
5b
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


200
190
180
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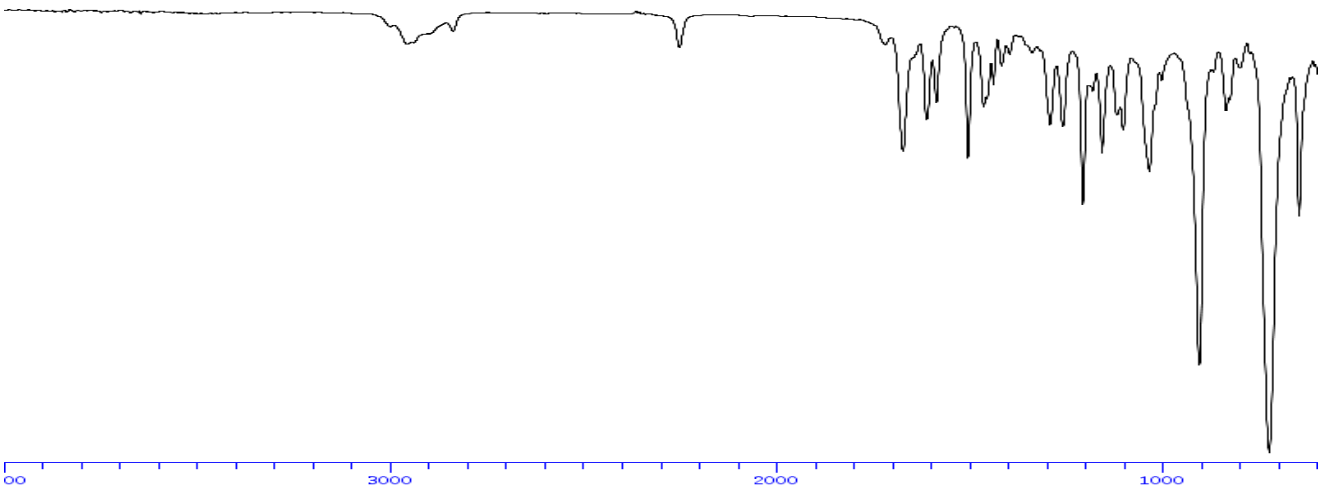
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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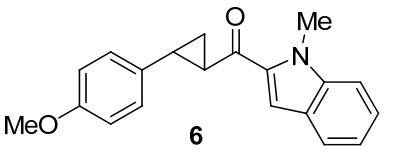
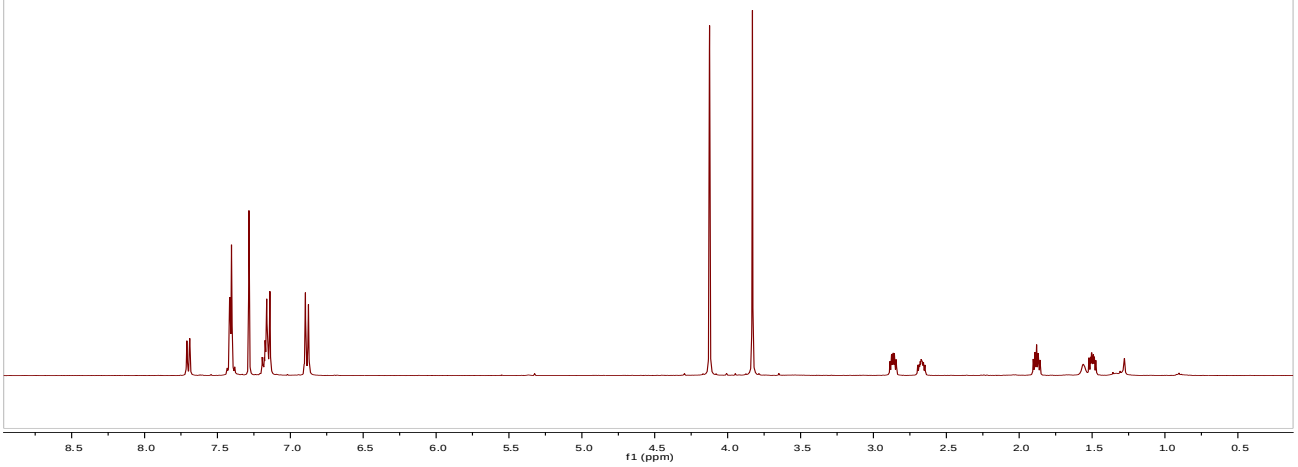
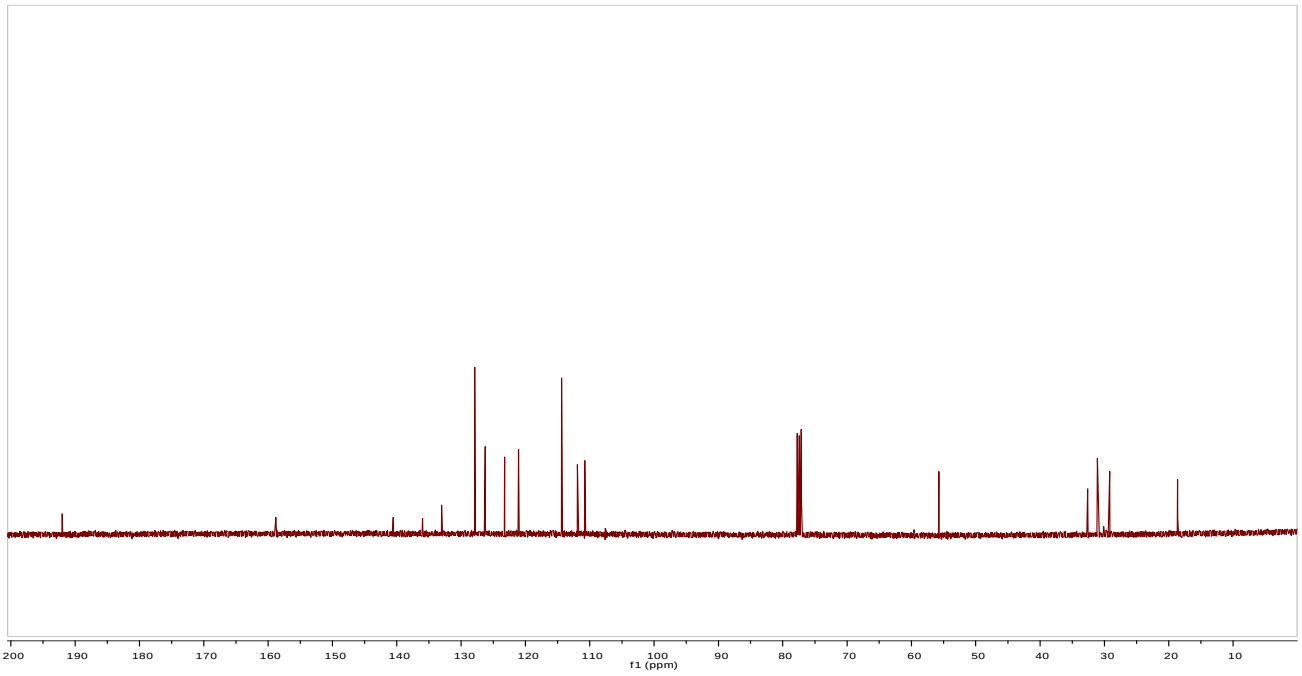

O
Me
N
MeO

6


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
f1 (ppm)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


200
190
180
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130
120
110
100
f1 (ppm)
90
80
70
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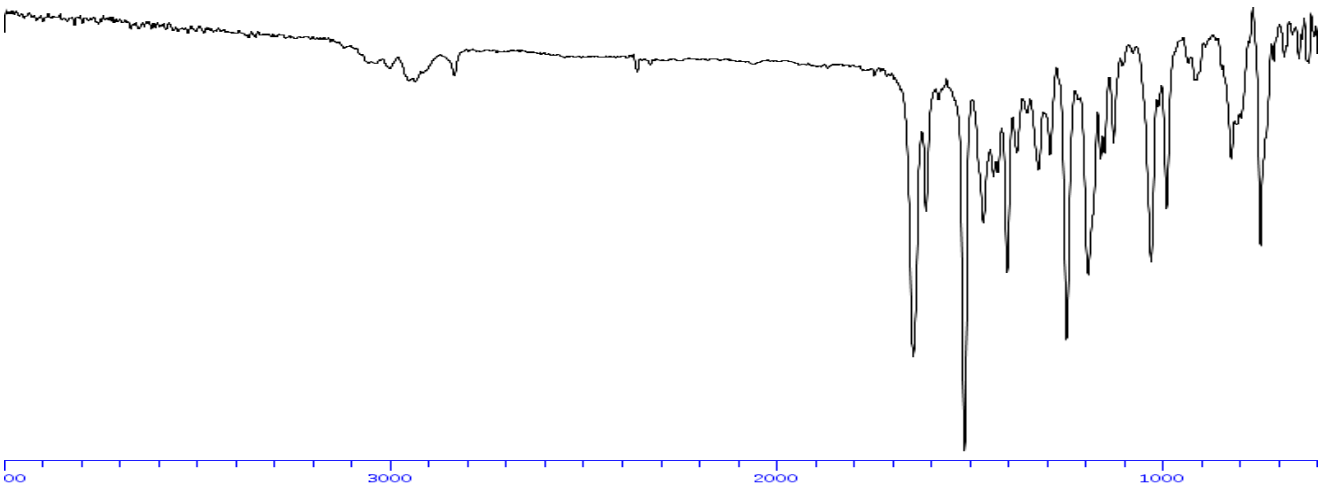
40
30
20
10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2000
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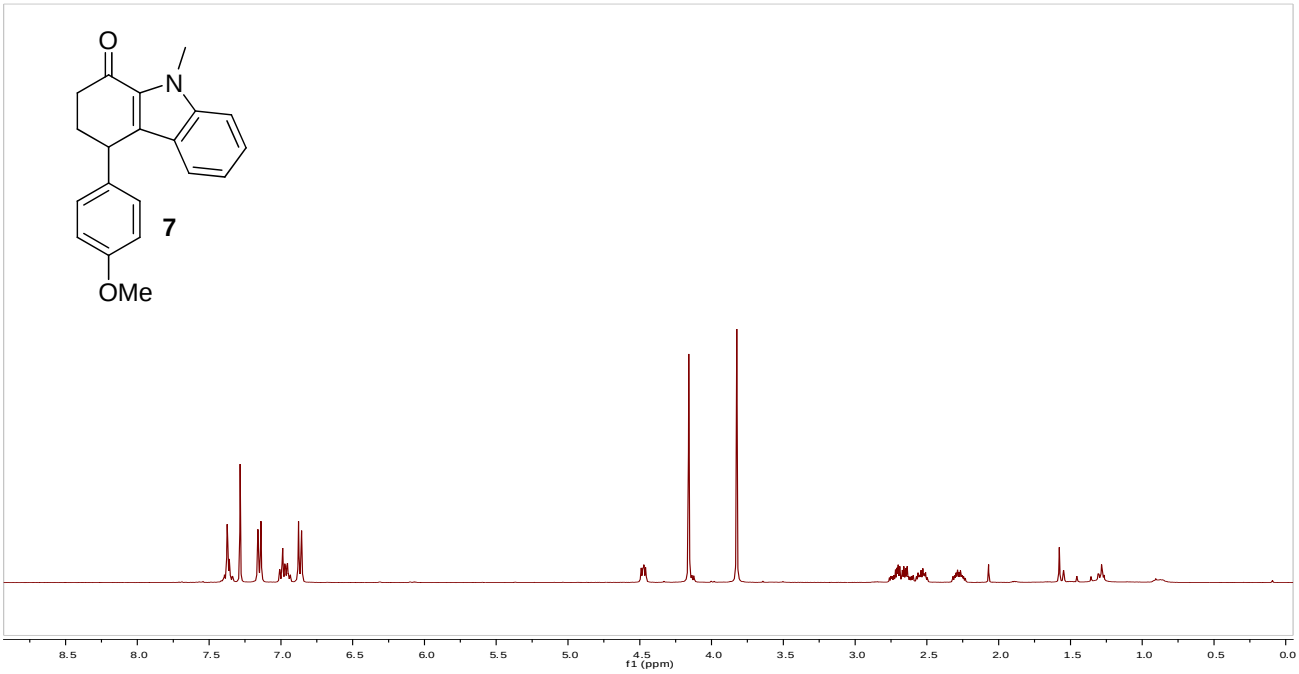
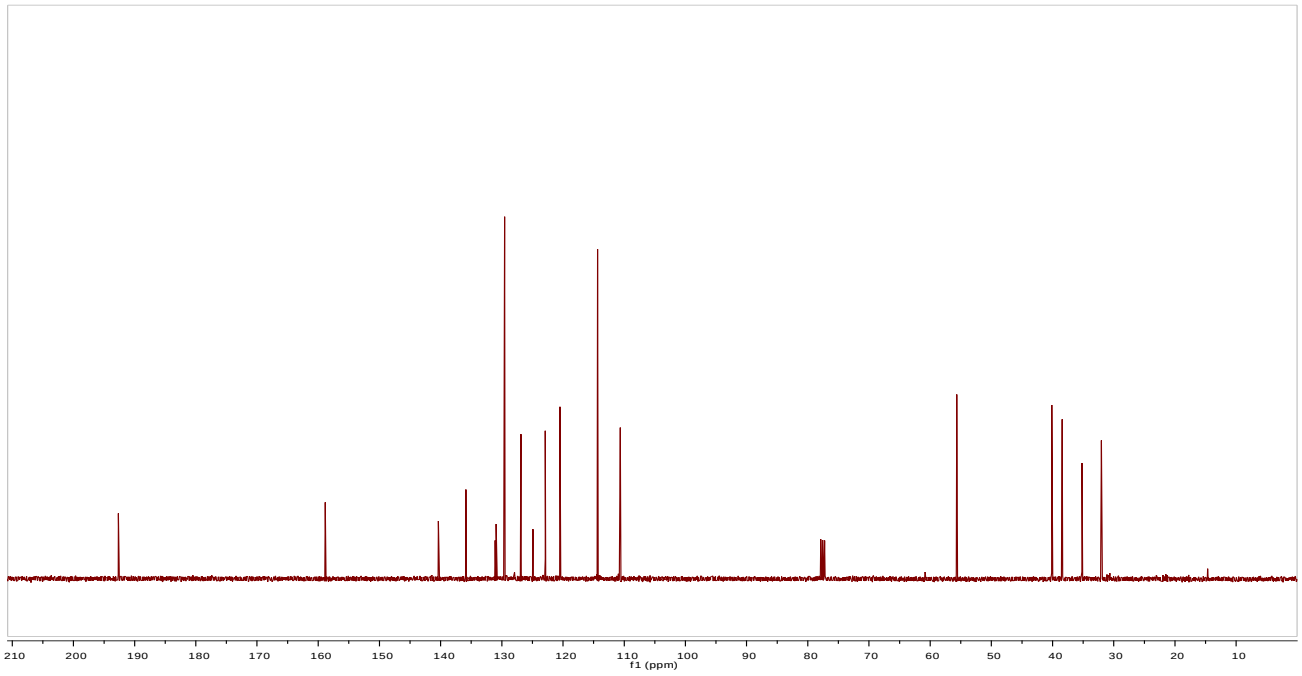

O
N
7
OMe
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


210
200
190
180
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100
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80
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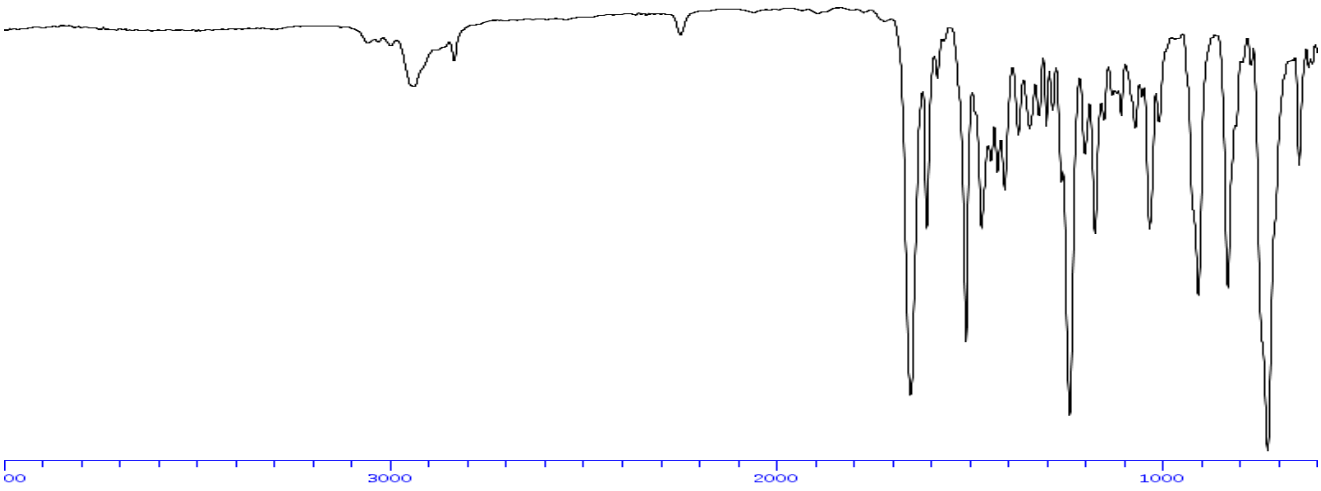
50
40
30
20
10
f1 (ppm)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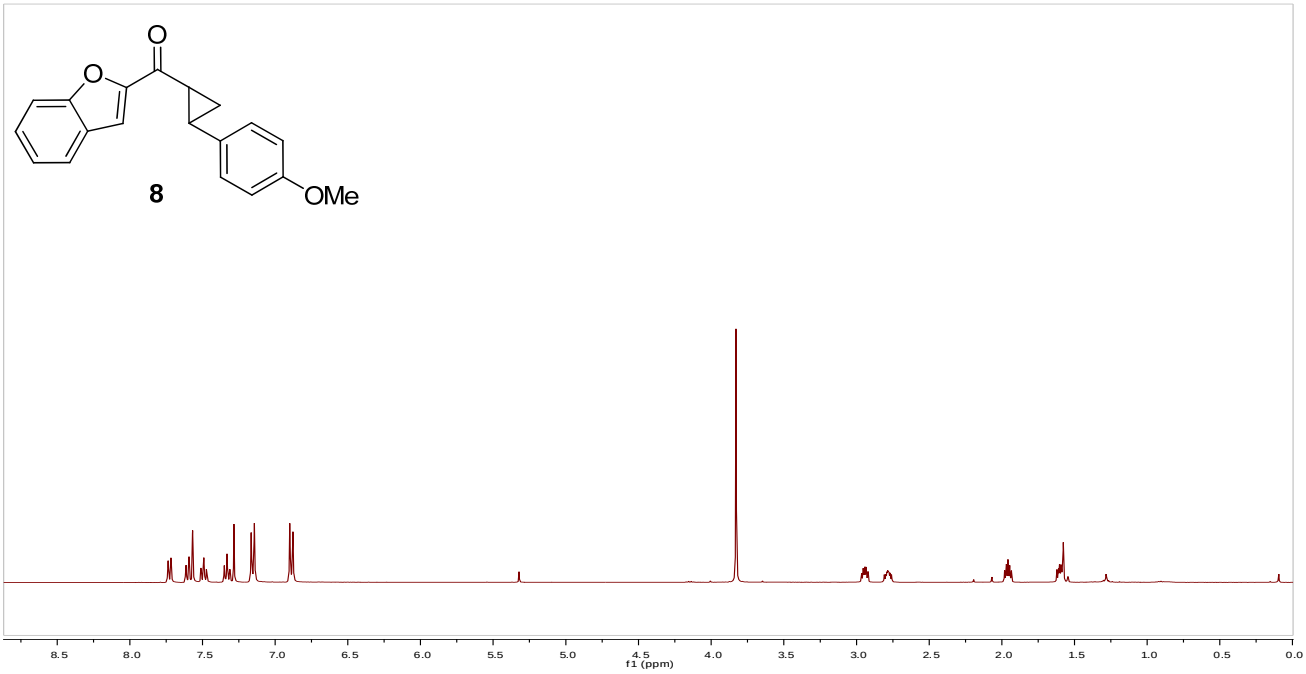
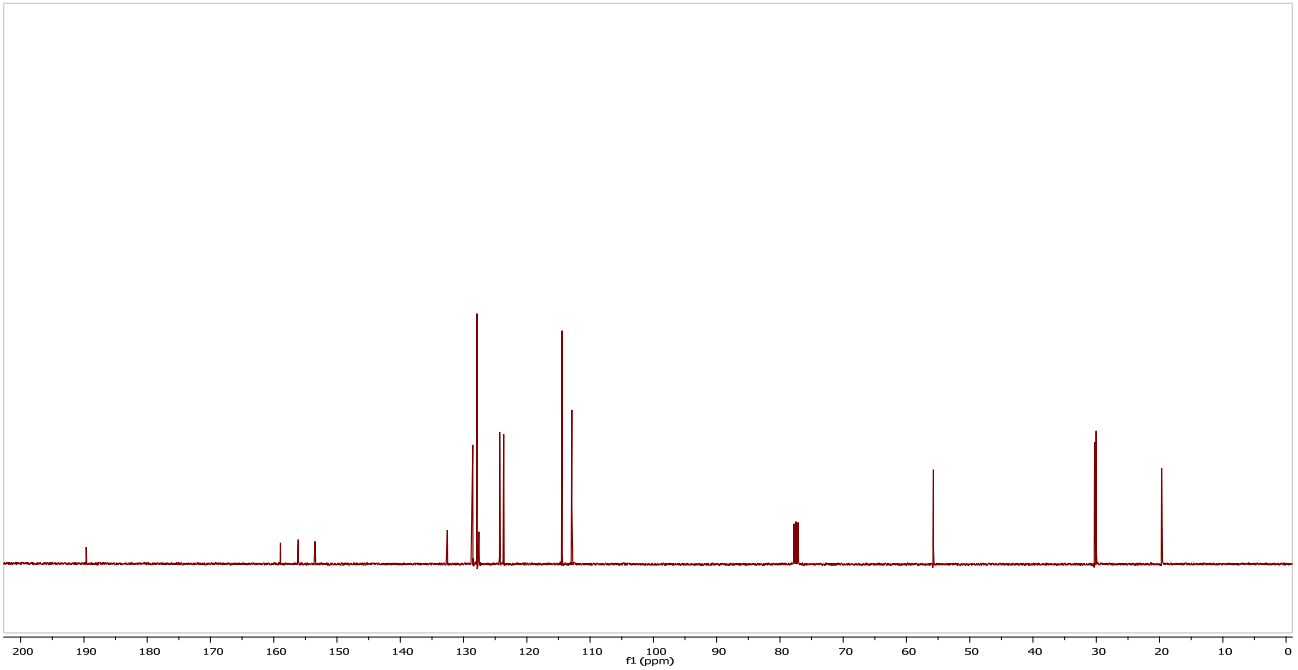

O
O
OMe
8
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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130
120
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100
90
80
70
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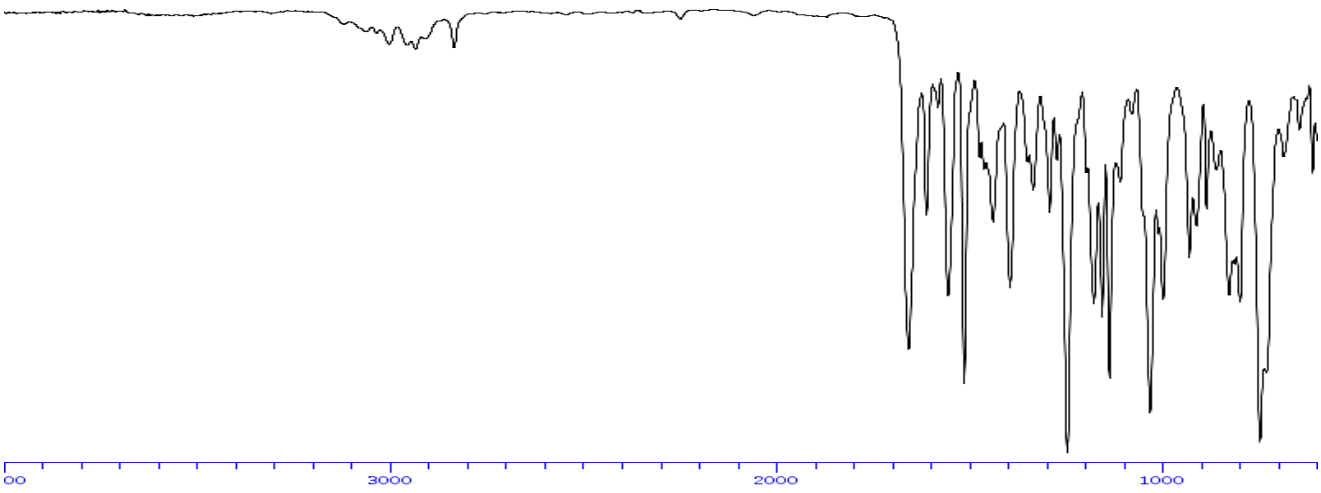
50
40
30
20
10
0
f1 (ppm)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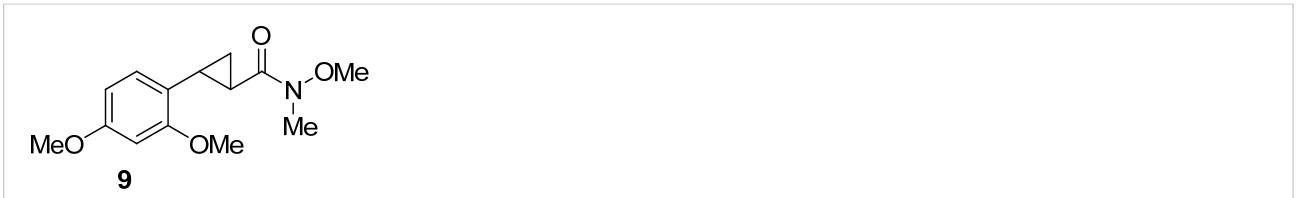
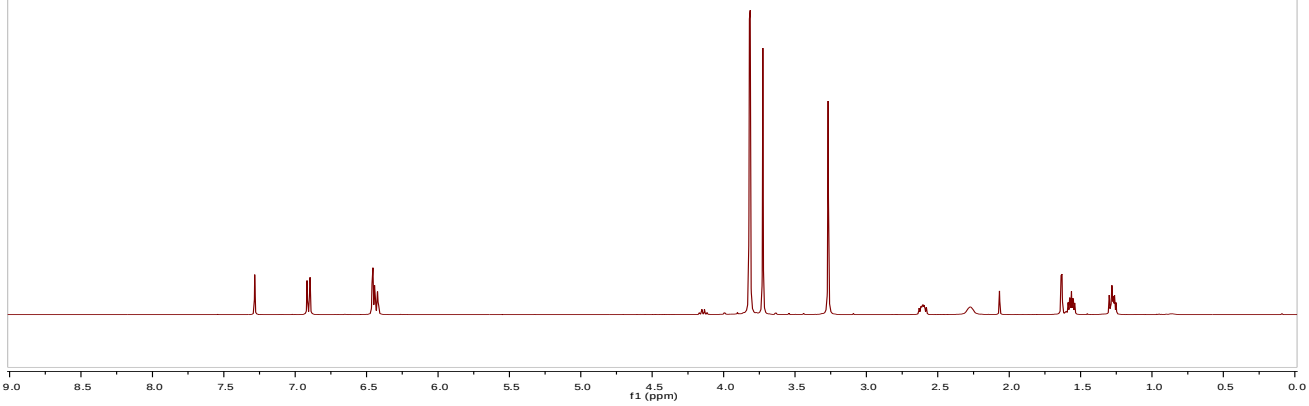
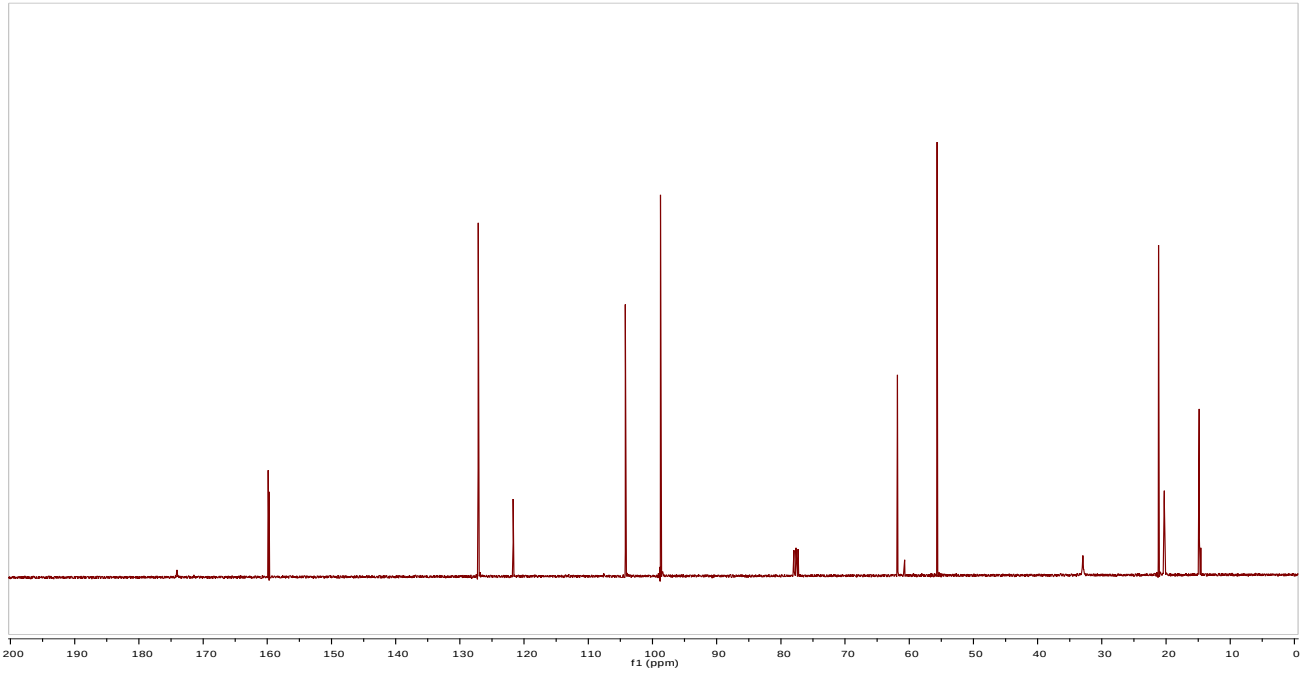

O
N
OMe
Me
MeO
OMe

9


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


200
190
180
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80
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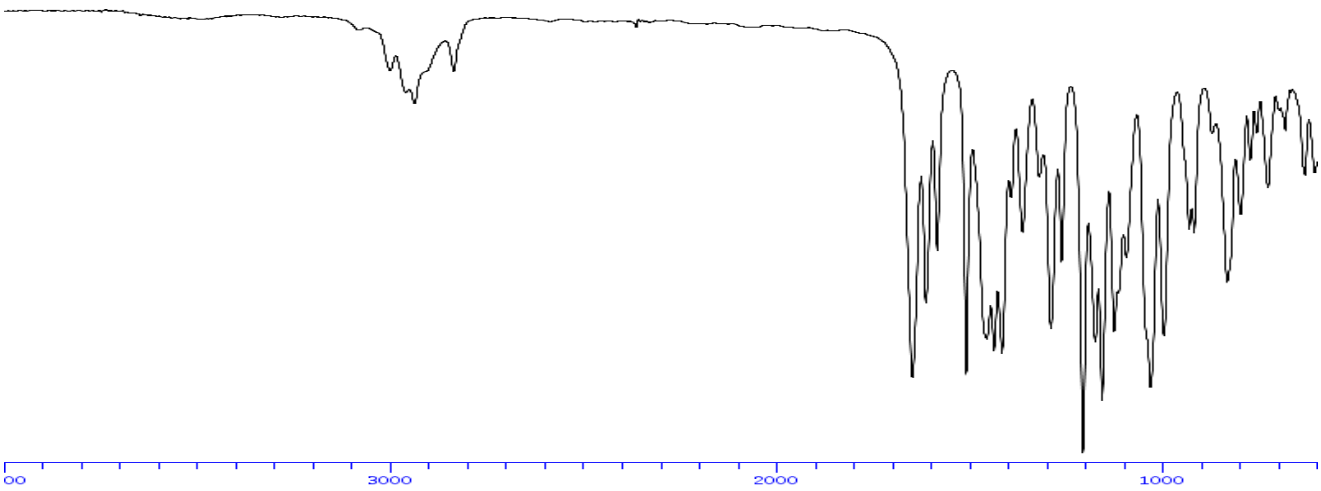
f1 (ppm)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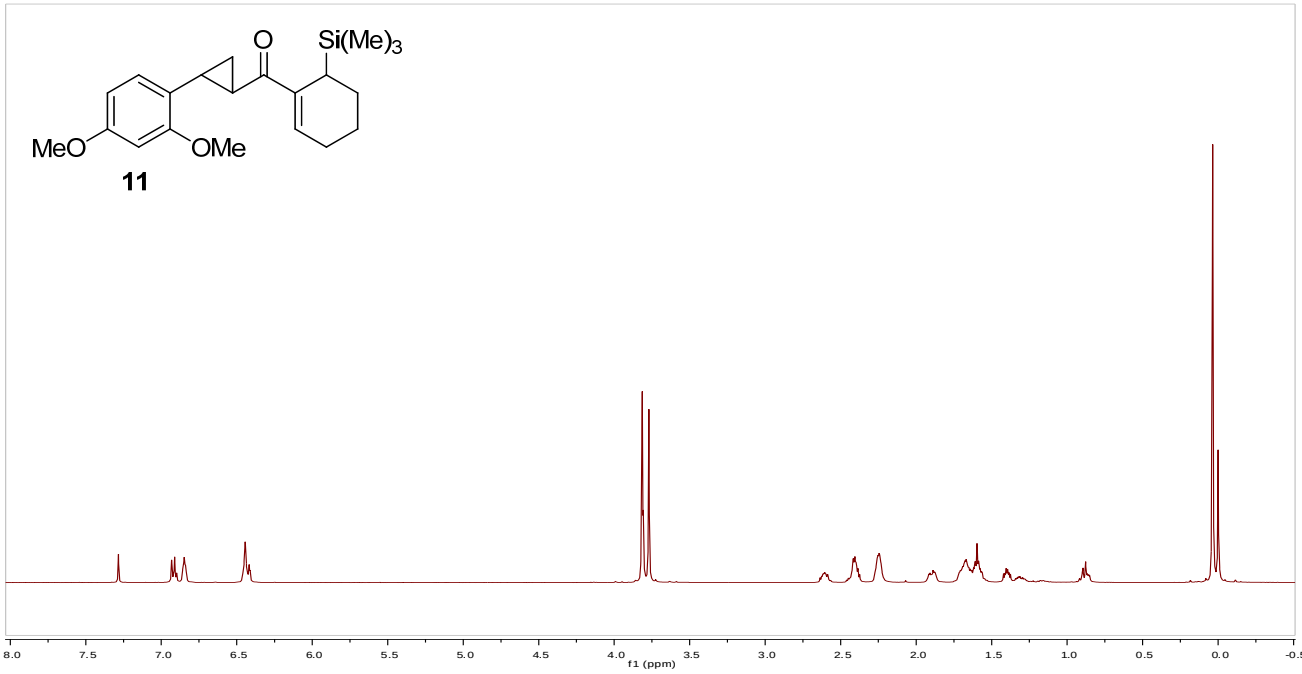
2000
1000


O
Si(Me)3
MeO
OMe
11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
2.5
2.0
1.5
1.0
0.5
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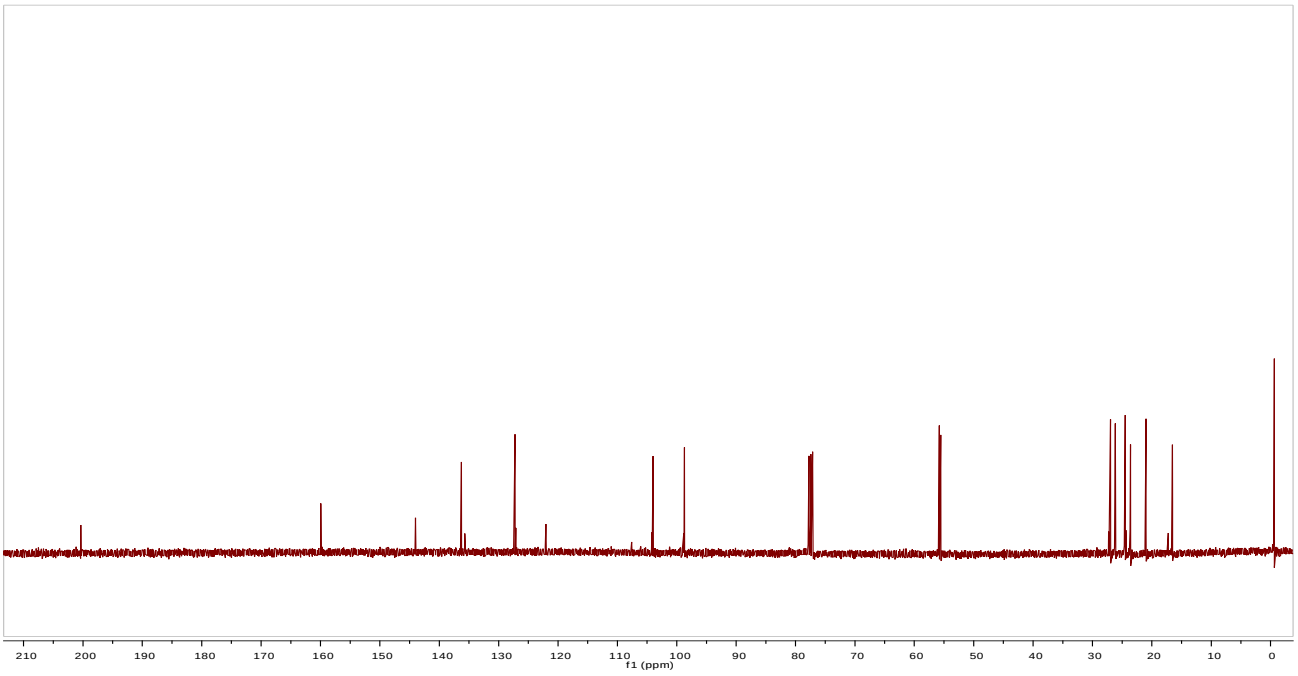
-0.5
f1 (ppm)


210
200
190
180
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90
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50
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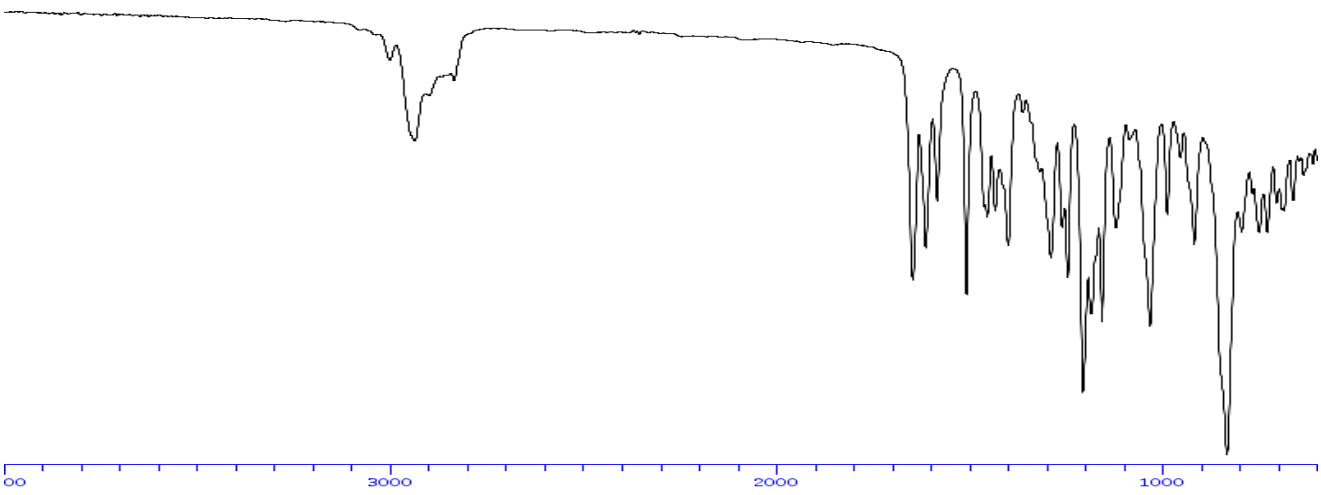
30
20
10
0
f1 (ppm)


00
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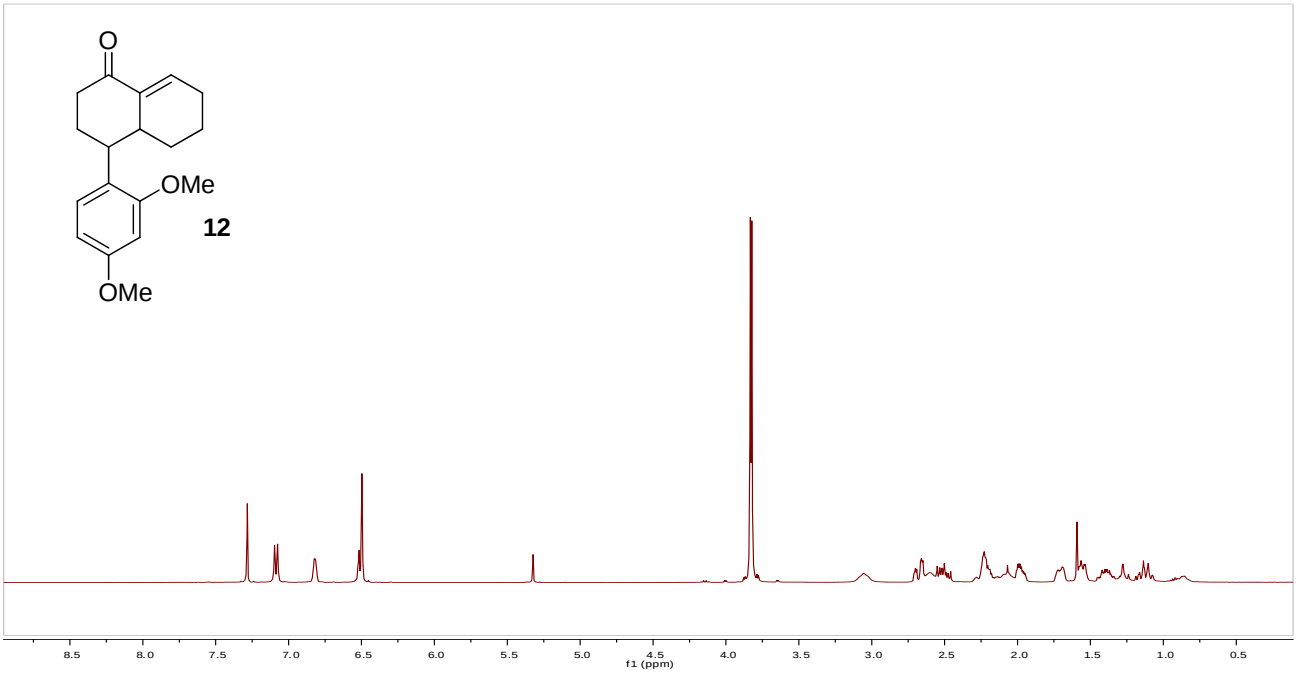
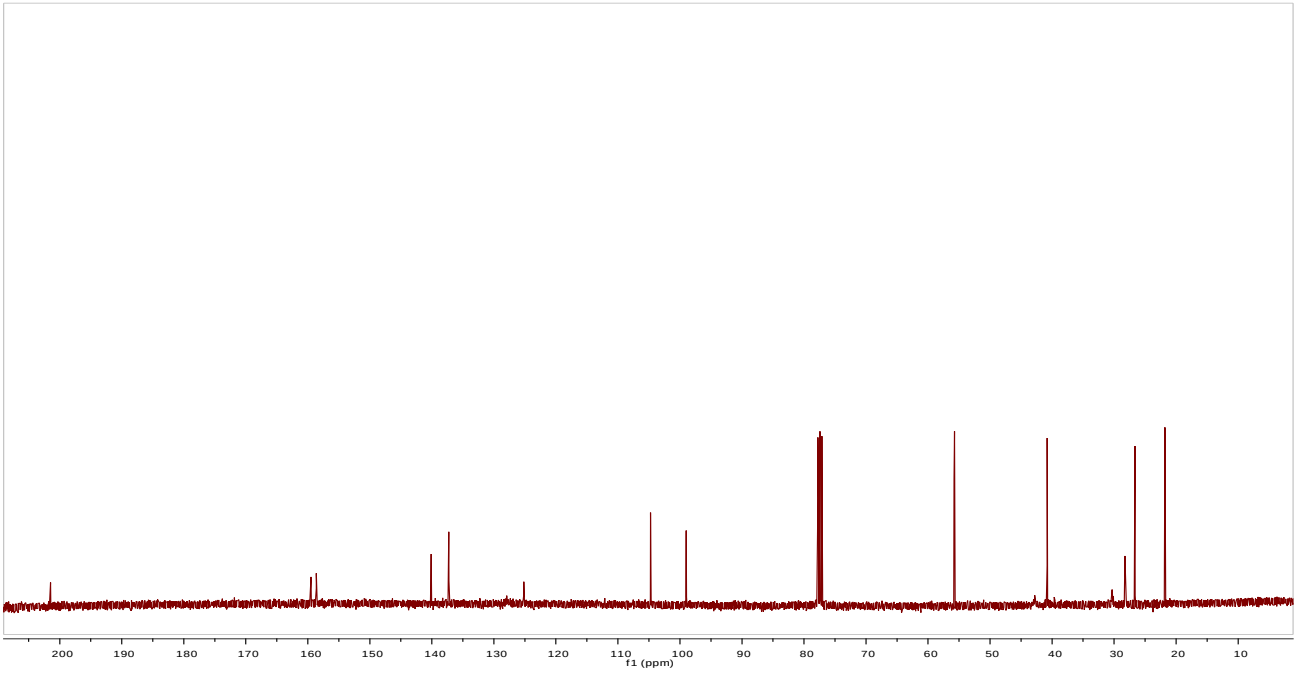
2000
1000


O
OMe
OMe
12
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


200
190
180
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140
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120
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100
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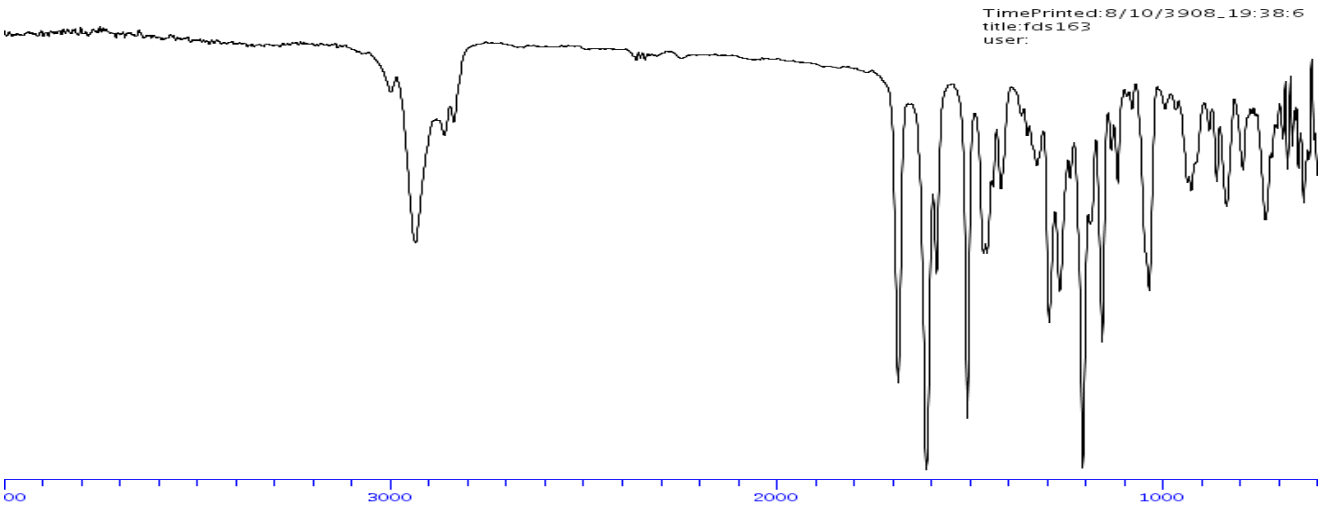
80
70
60
50
40
30
20
10
f1 (ppm)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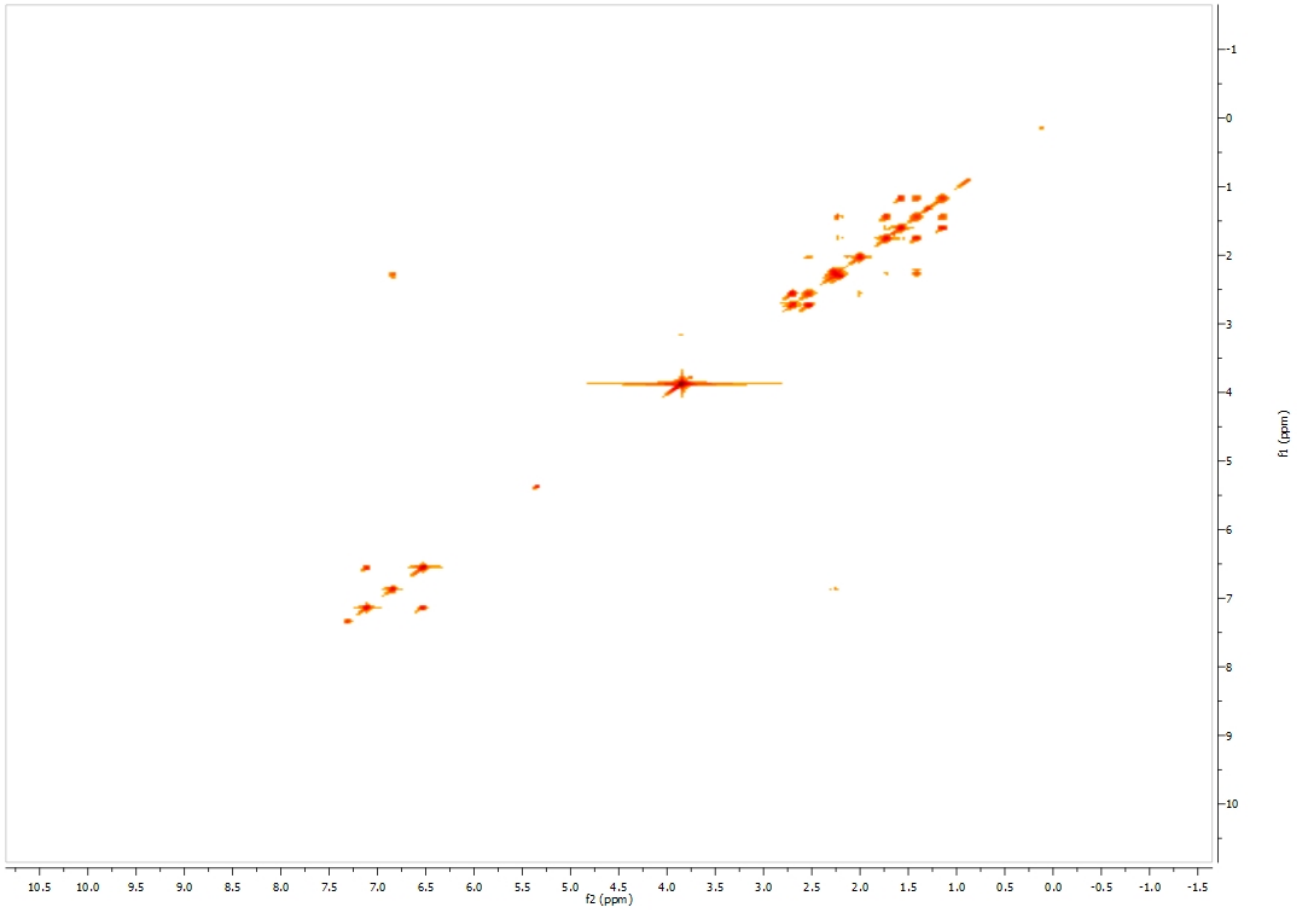
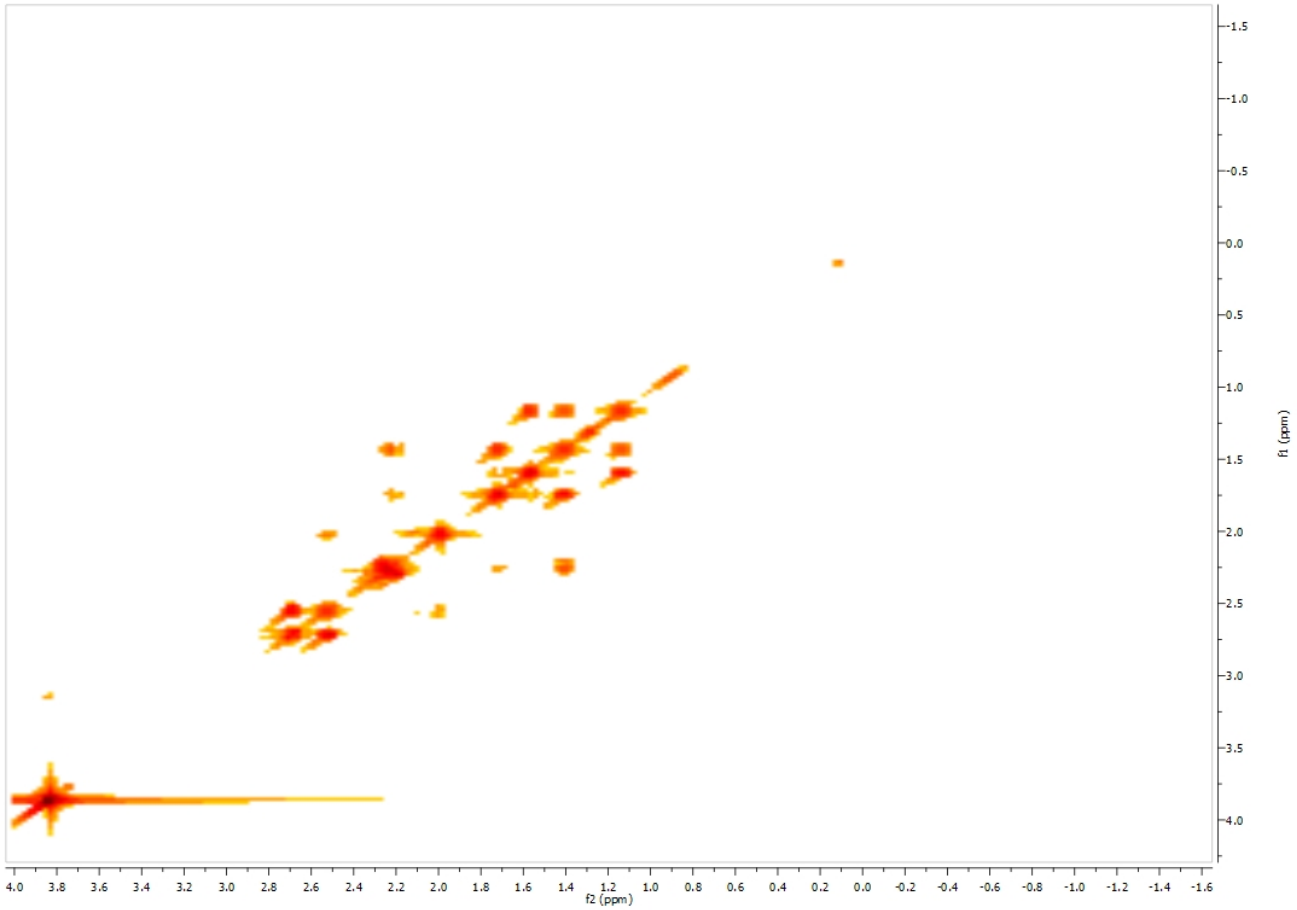
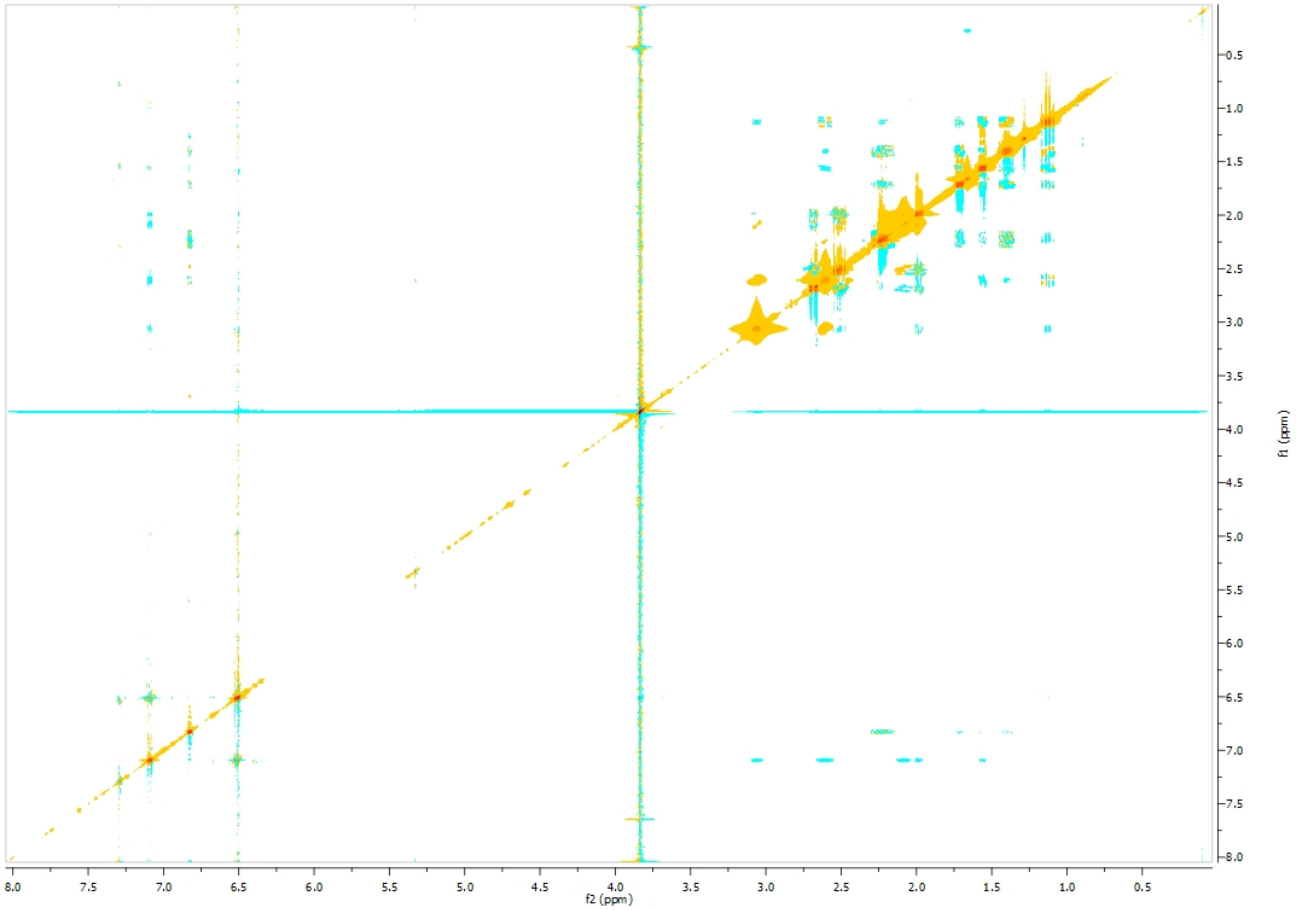
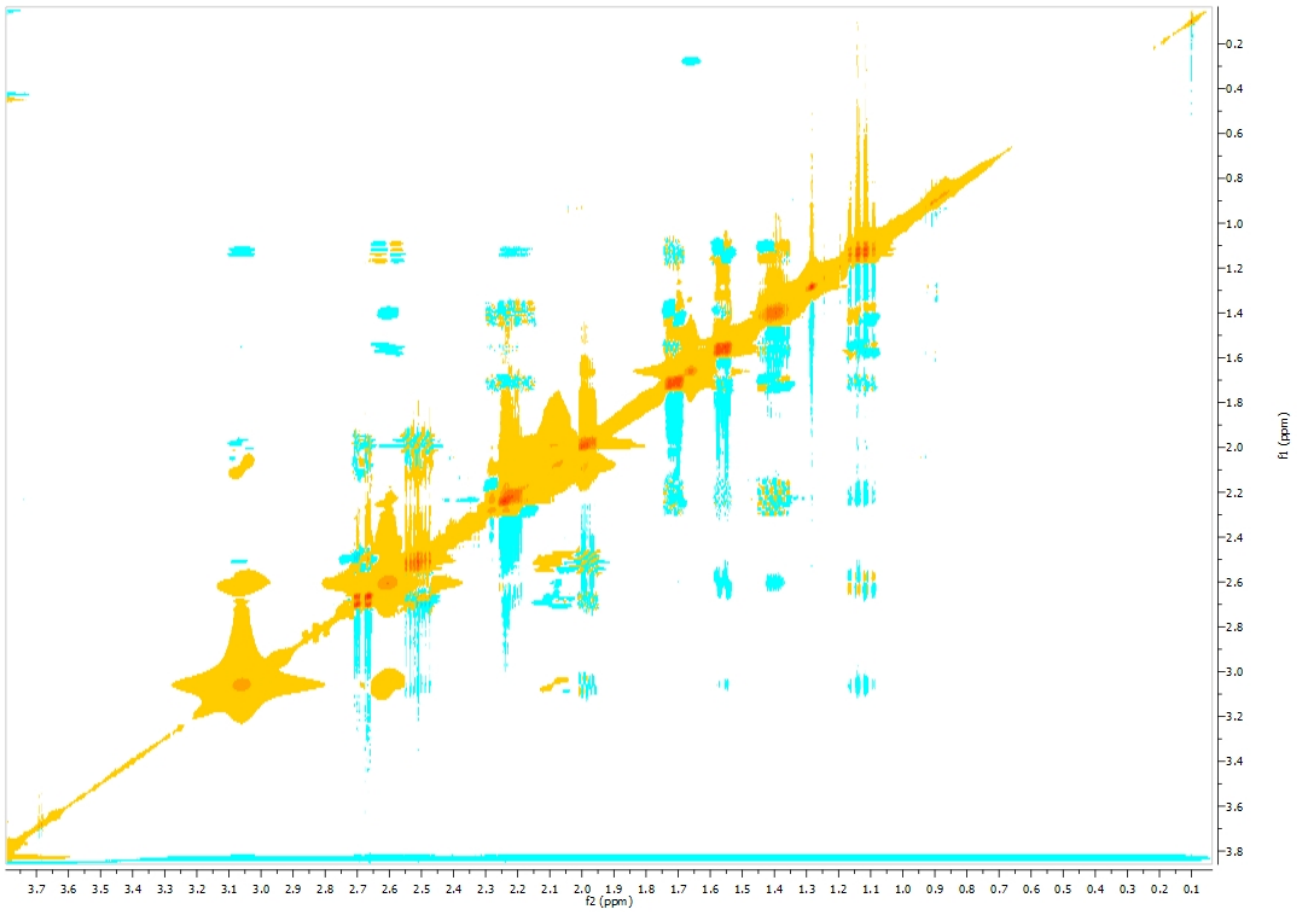
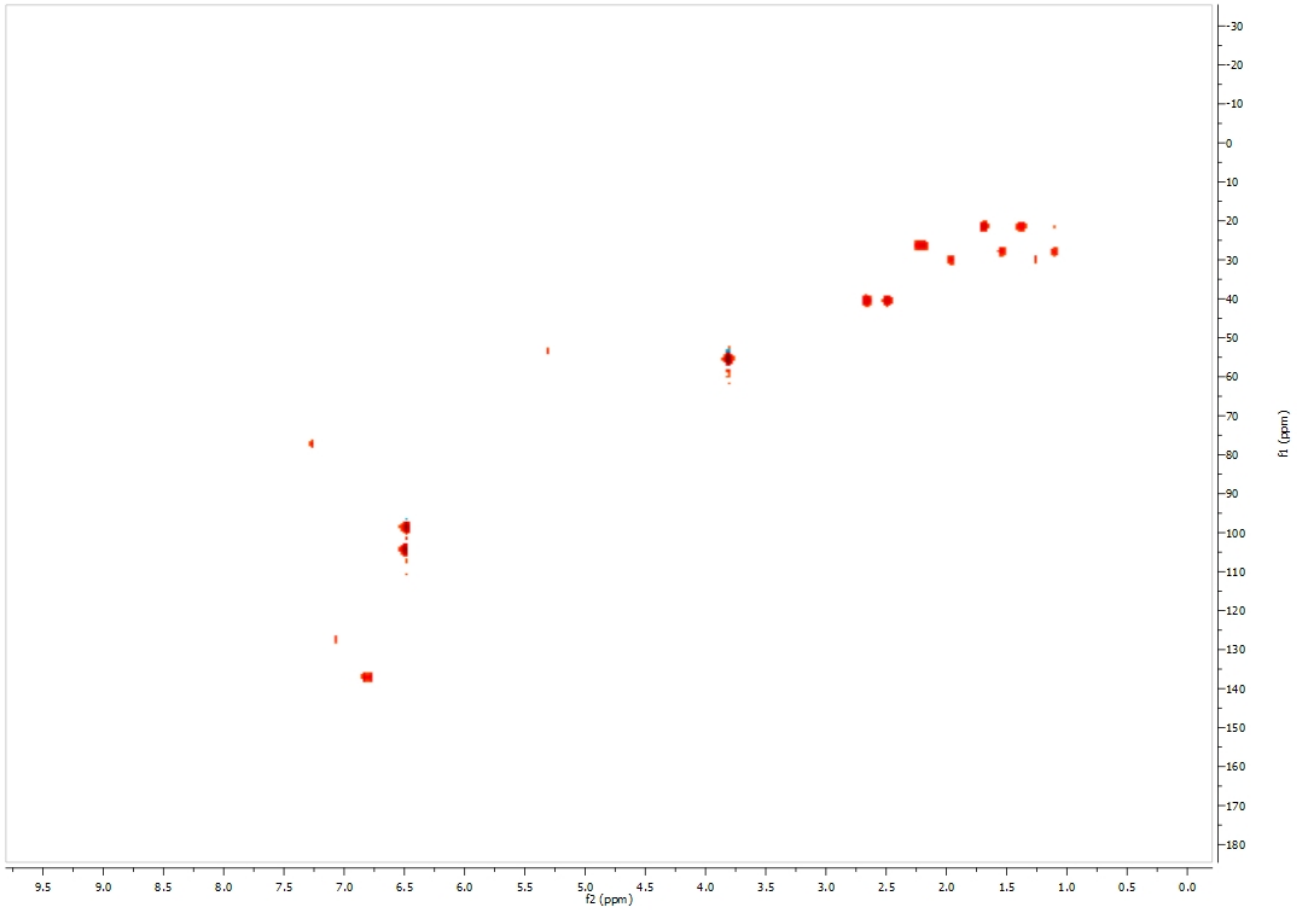
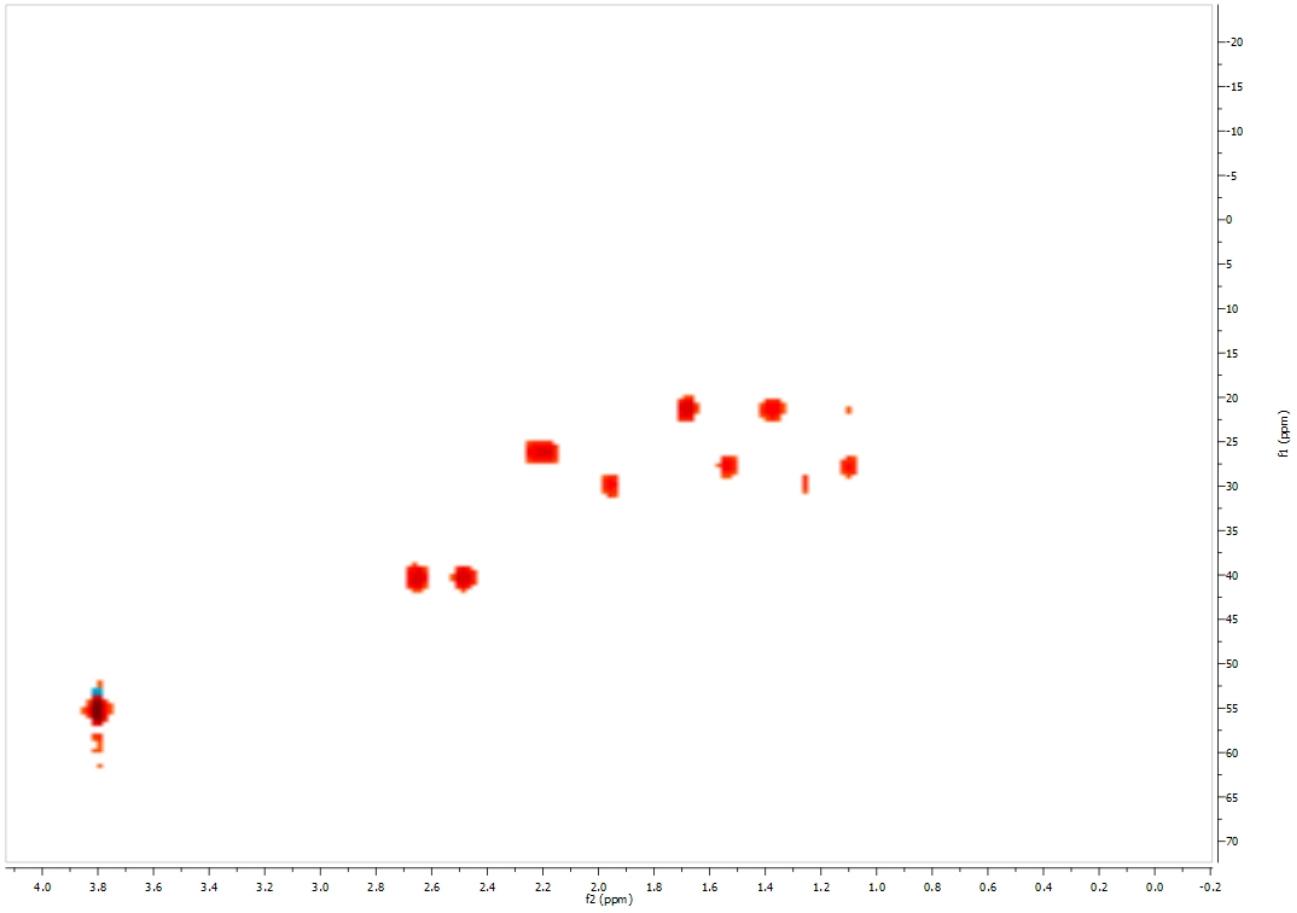

f1 (ppm)
f2 (ppm)

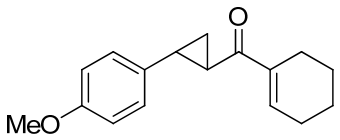

f1 (ppm)
f2 (ppm)


f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)


f2 (ppm)
f1 (ppm)


O
MeO

15

7
6
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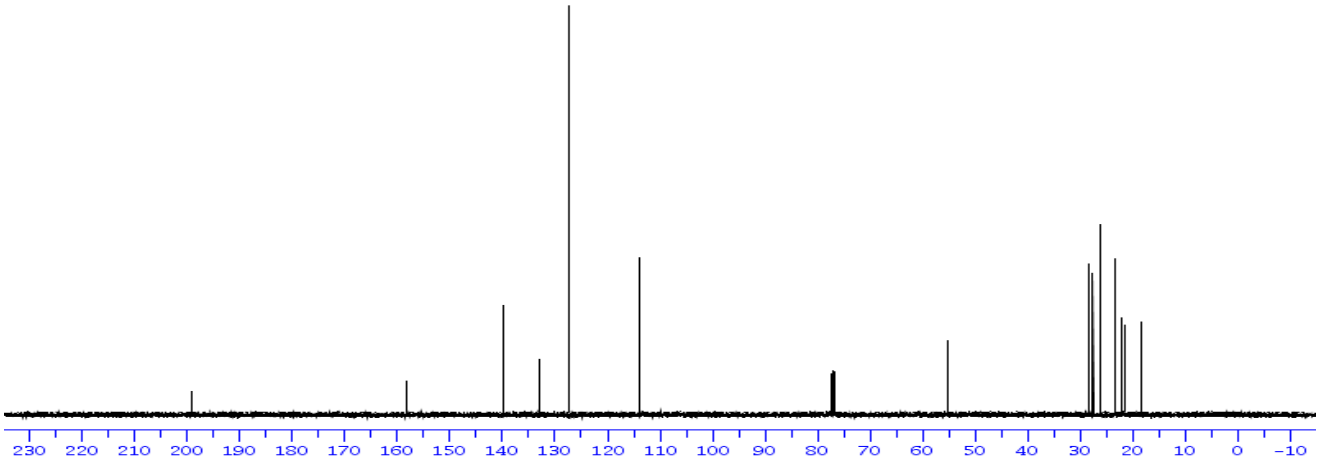
3
2
1
0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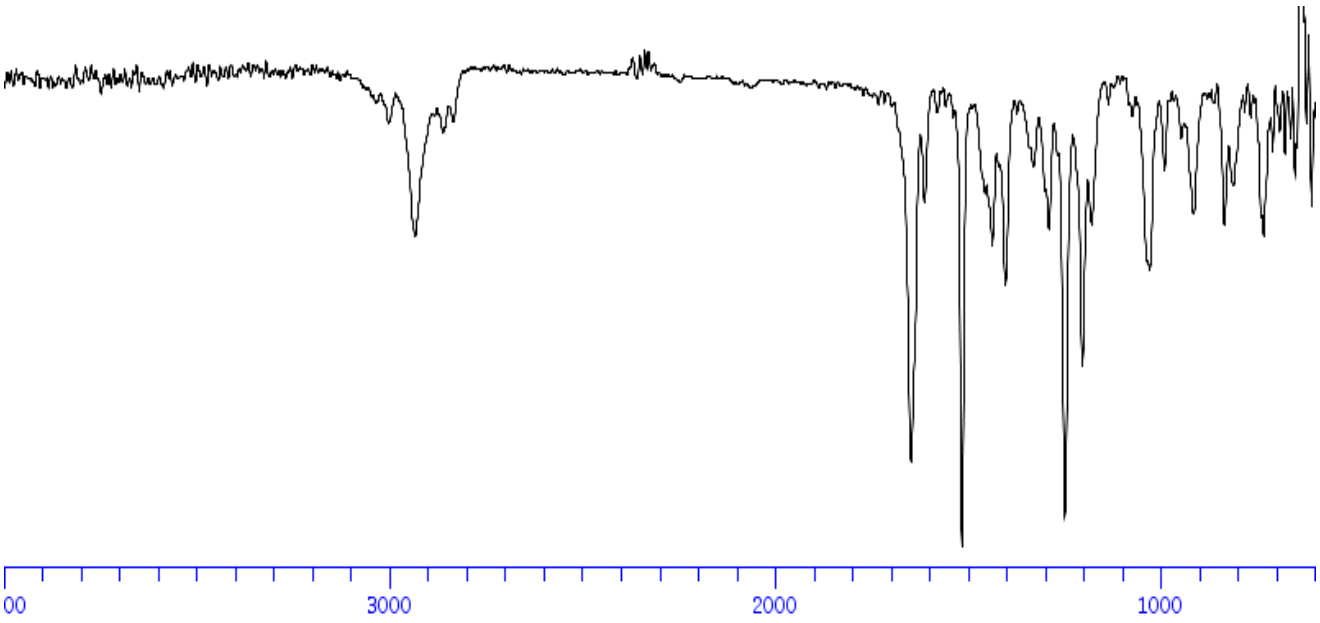
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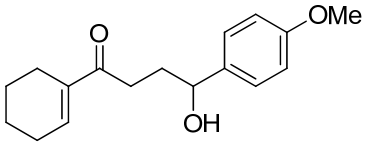
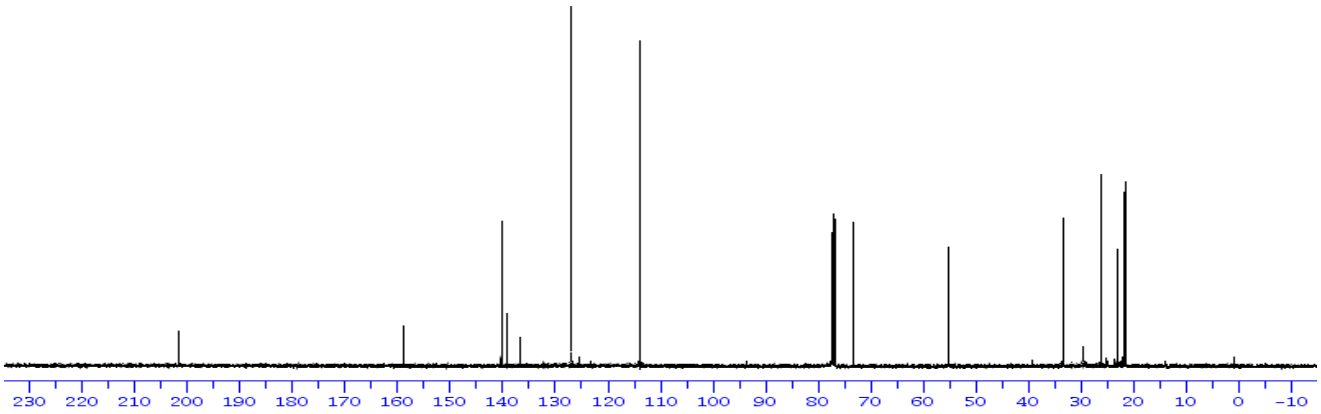

O
OMe
OH

16

7
6
5
4
3
2
1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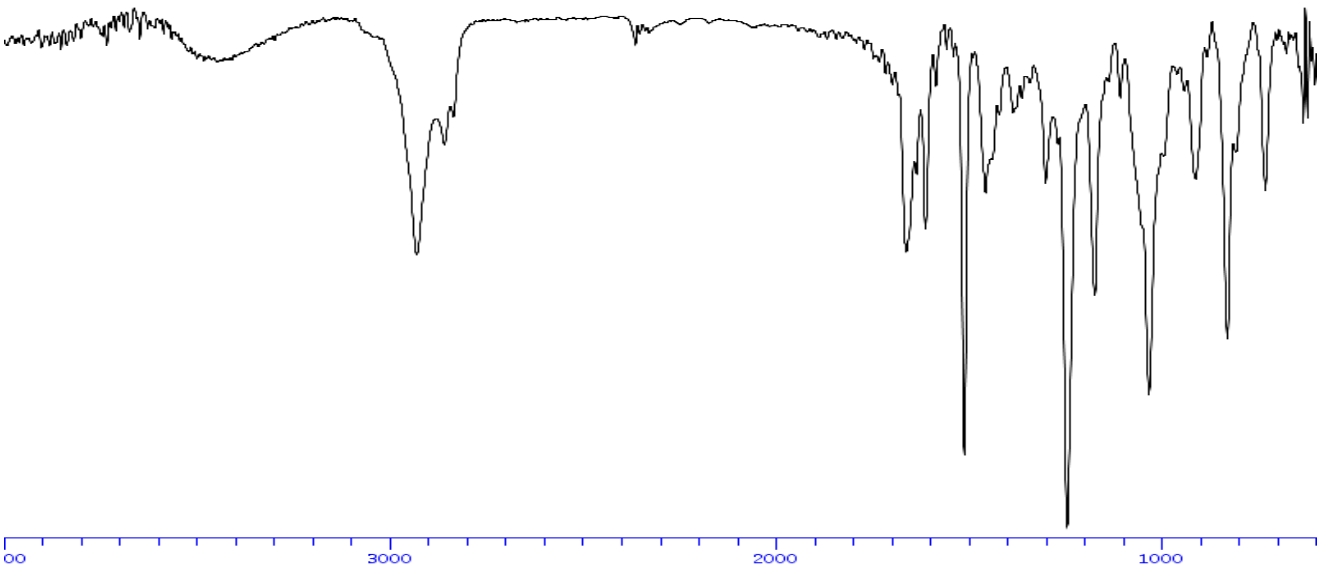
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2000
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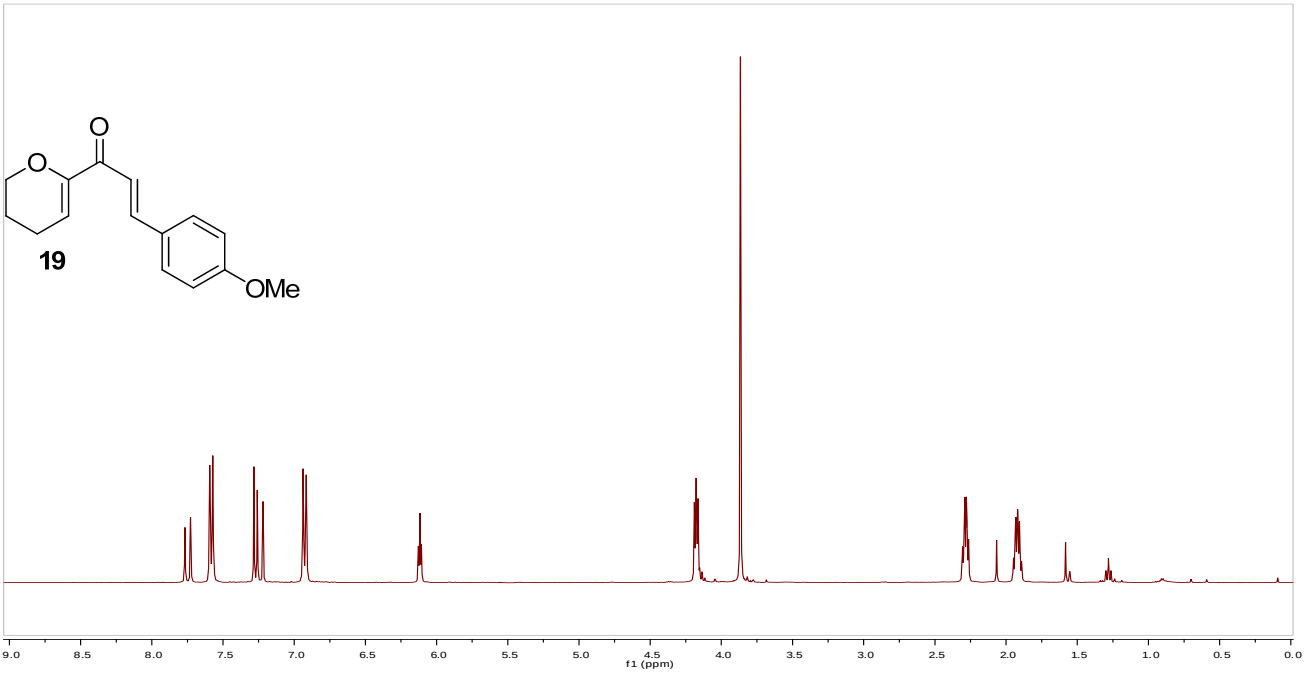
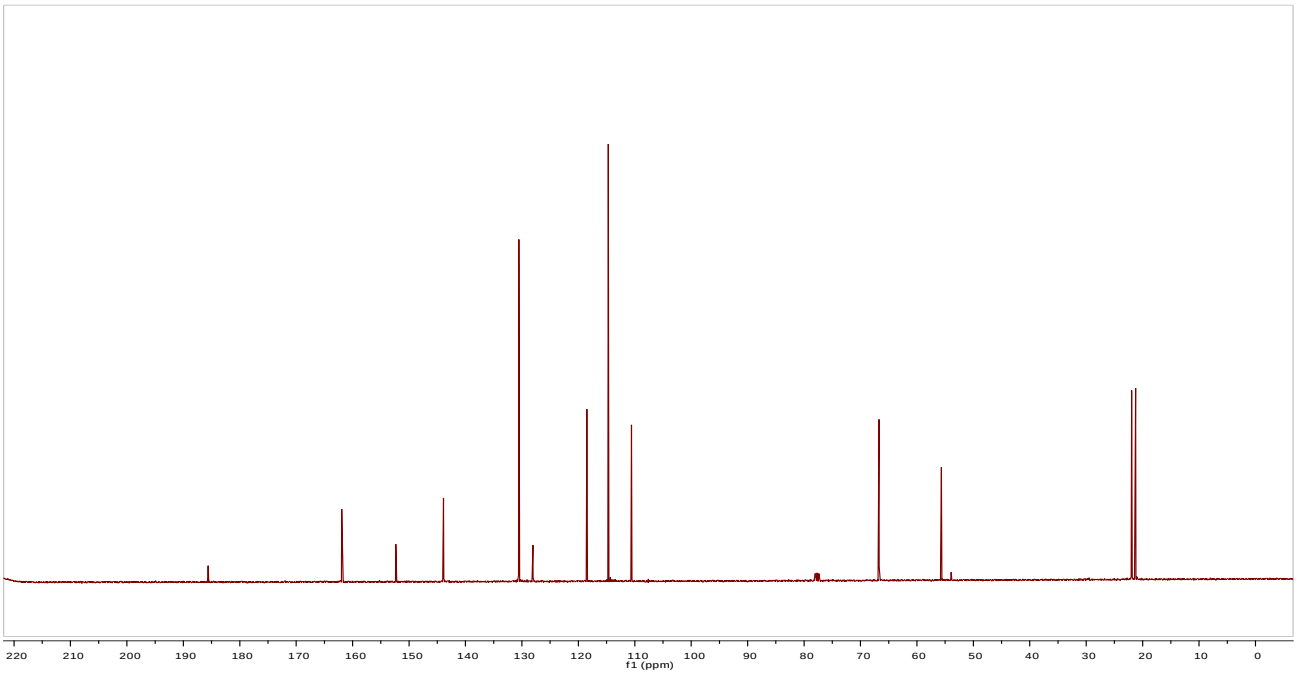
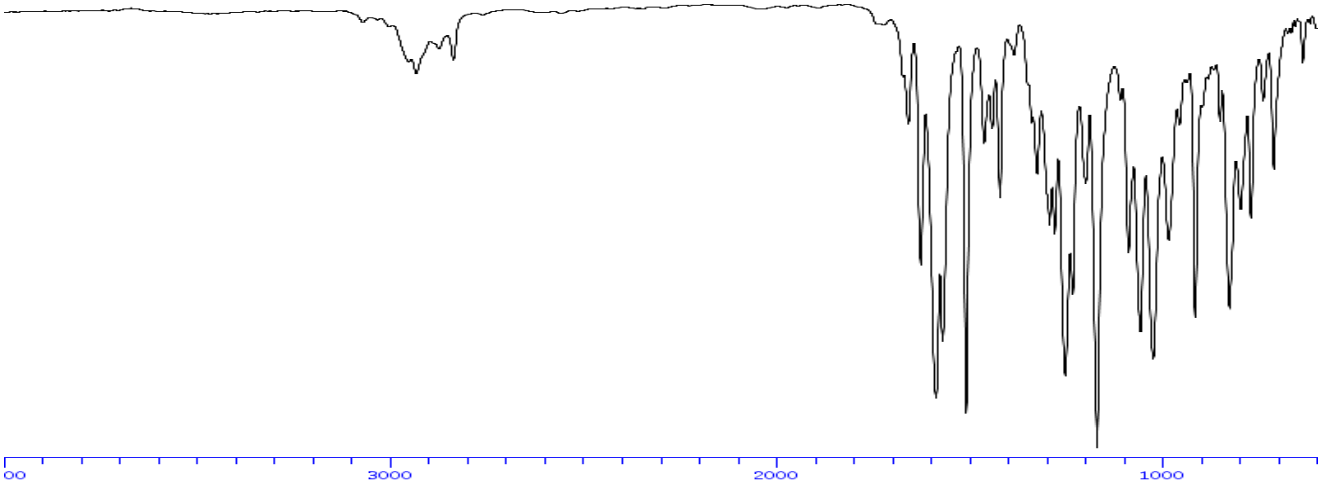

O
O
19
OMe
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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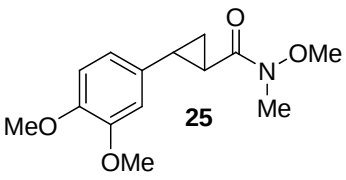
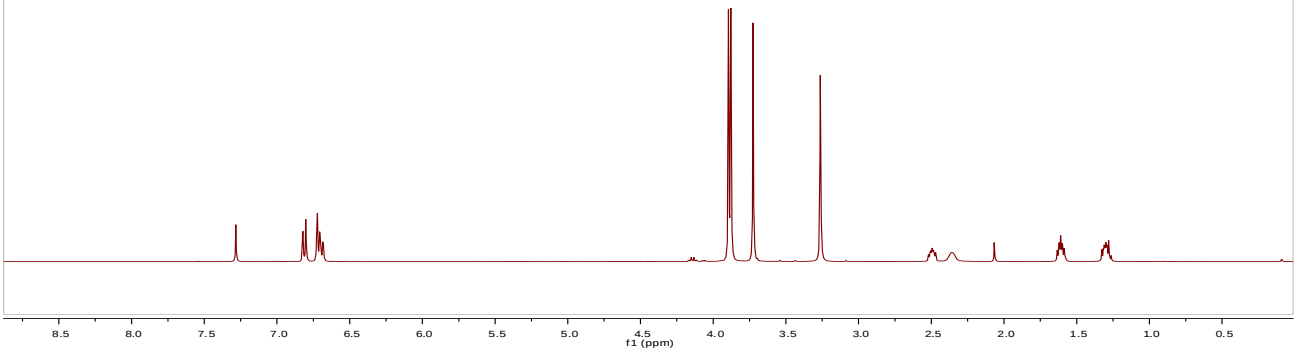
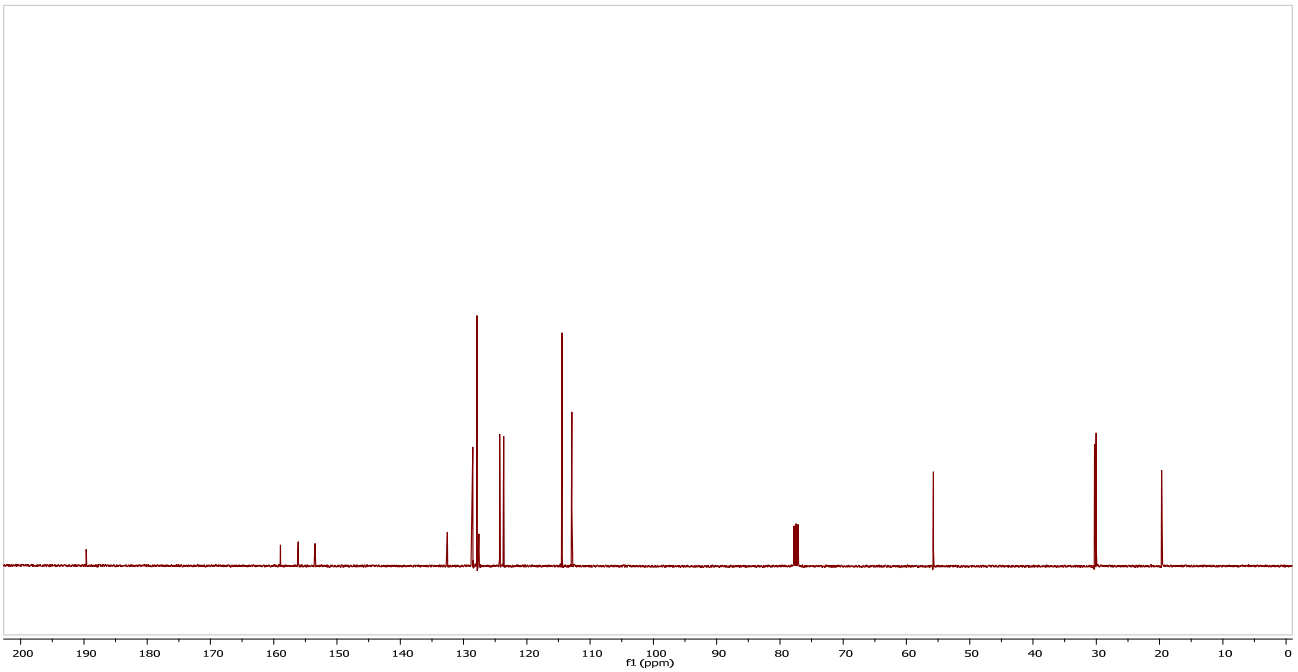
3000
2000
1000


O
N
OMe
Me
MeO
OMe

25


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


200
190
180
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130
120
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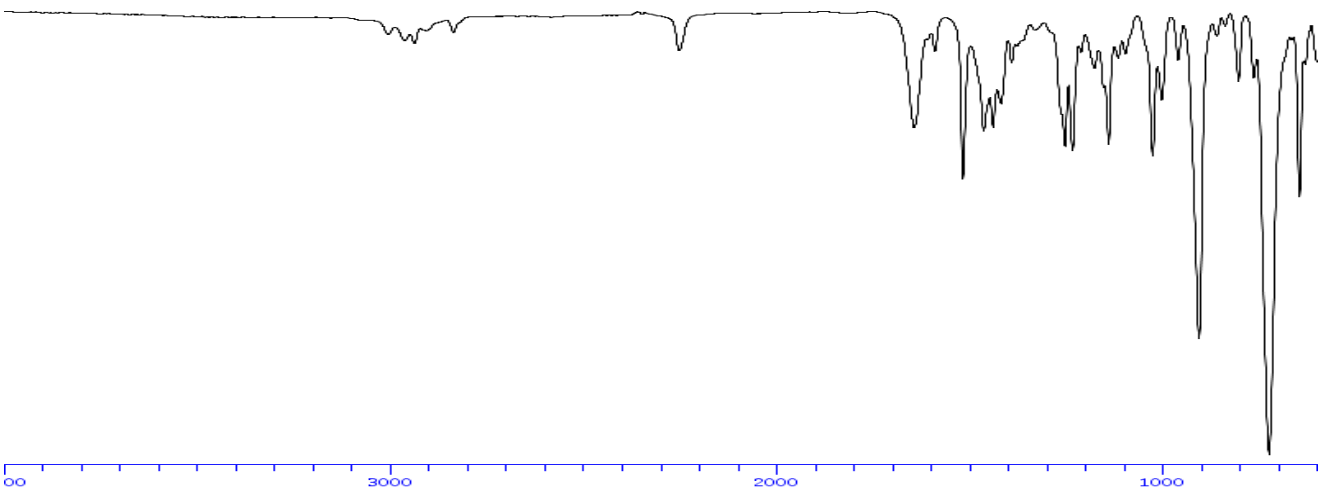
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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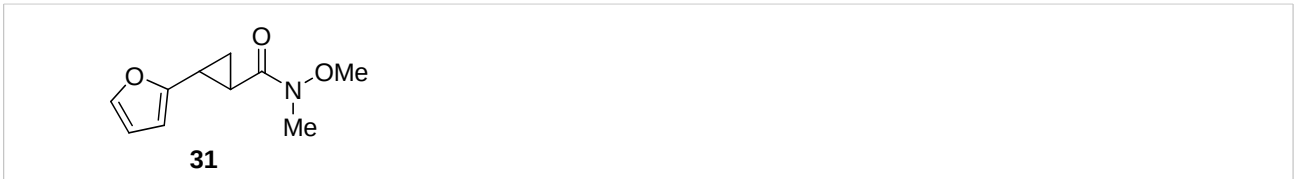
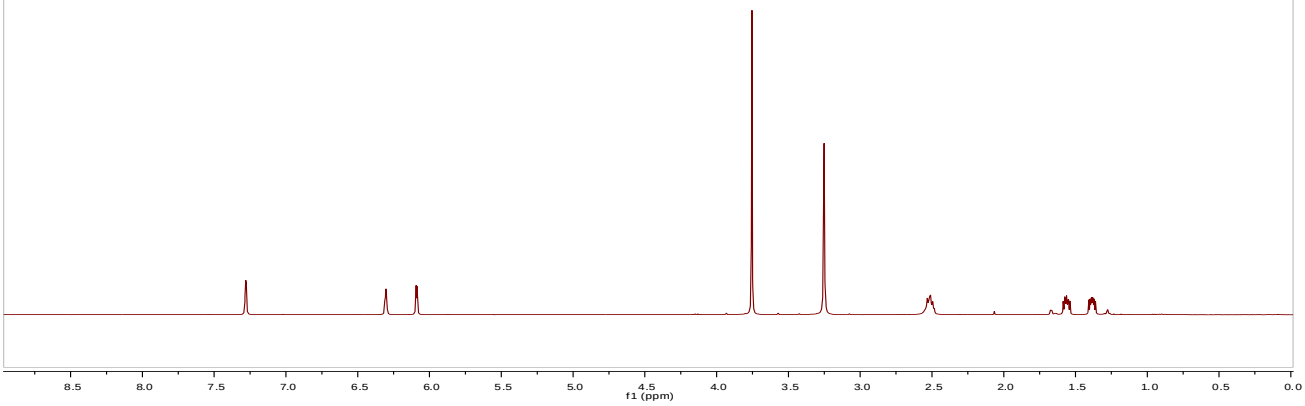
2000
1000


O
O
N
OMe
Me

31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7.5
7.0
6.5
6.0
5.5
5.0
4.5
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2.5
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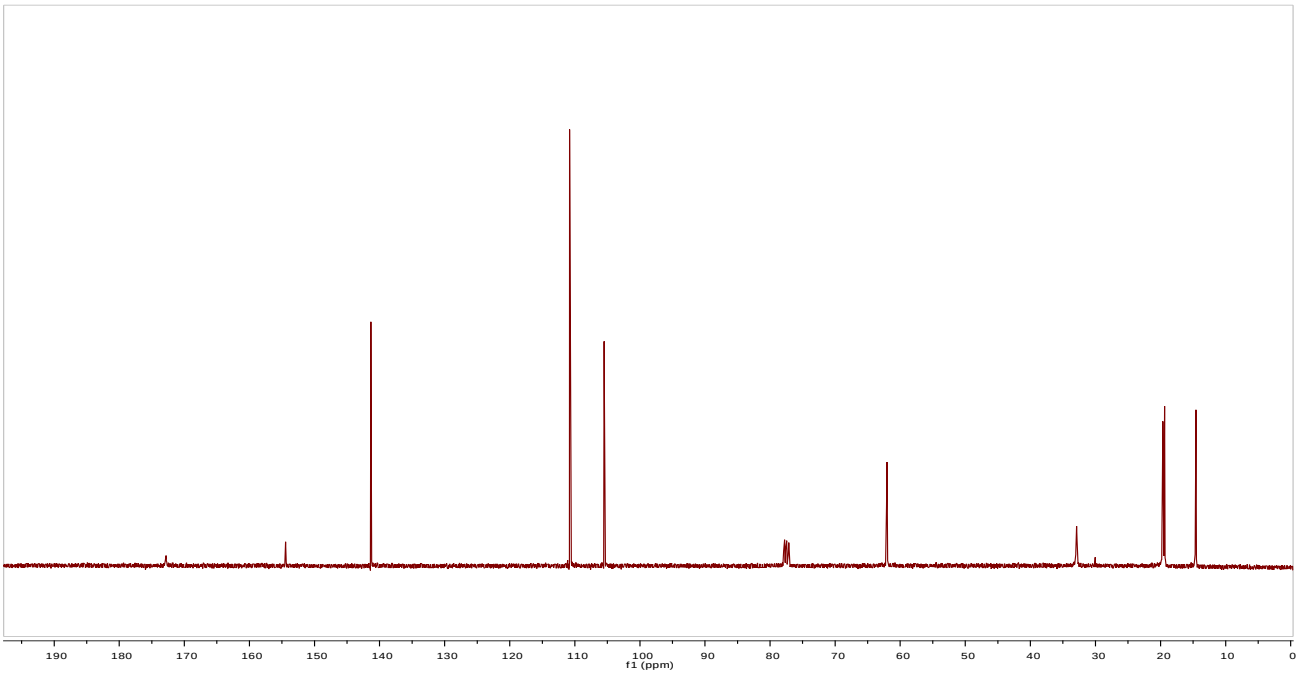
1.5
1.0
0.5
0.0
f1 (ppm)


190
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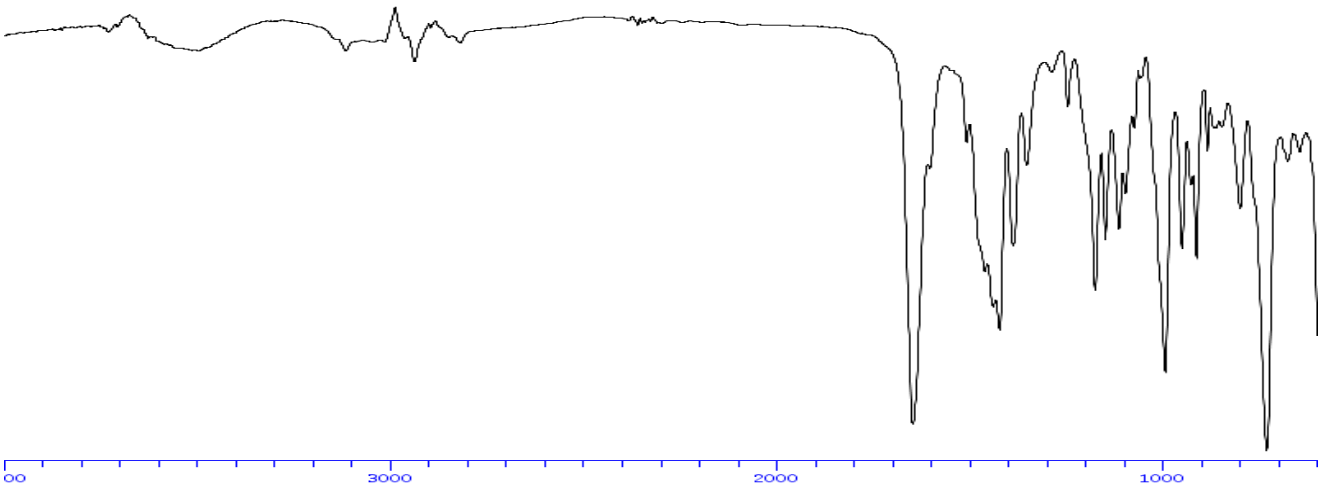
f1 (ppm)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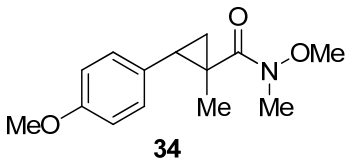
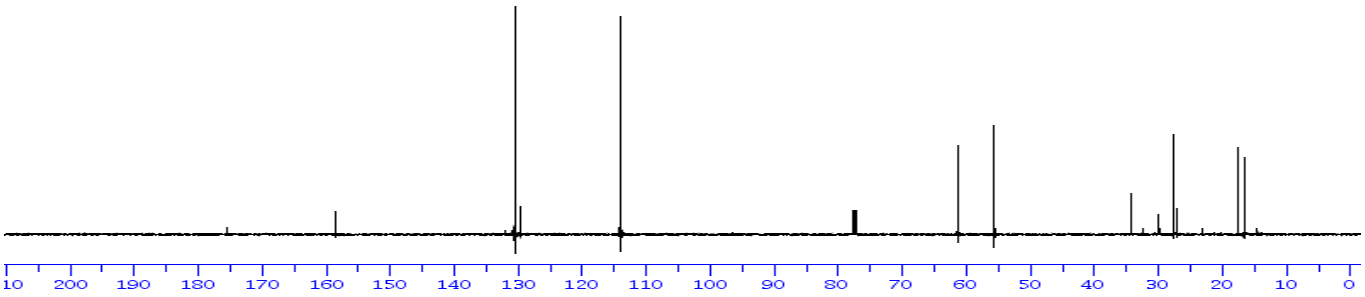

O
OMe
N
Me
Me
MeO

34

7
6
5
4
3
2
1
0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10
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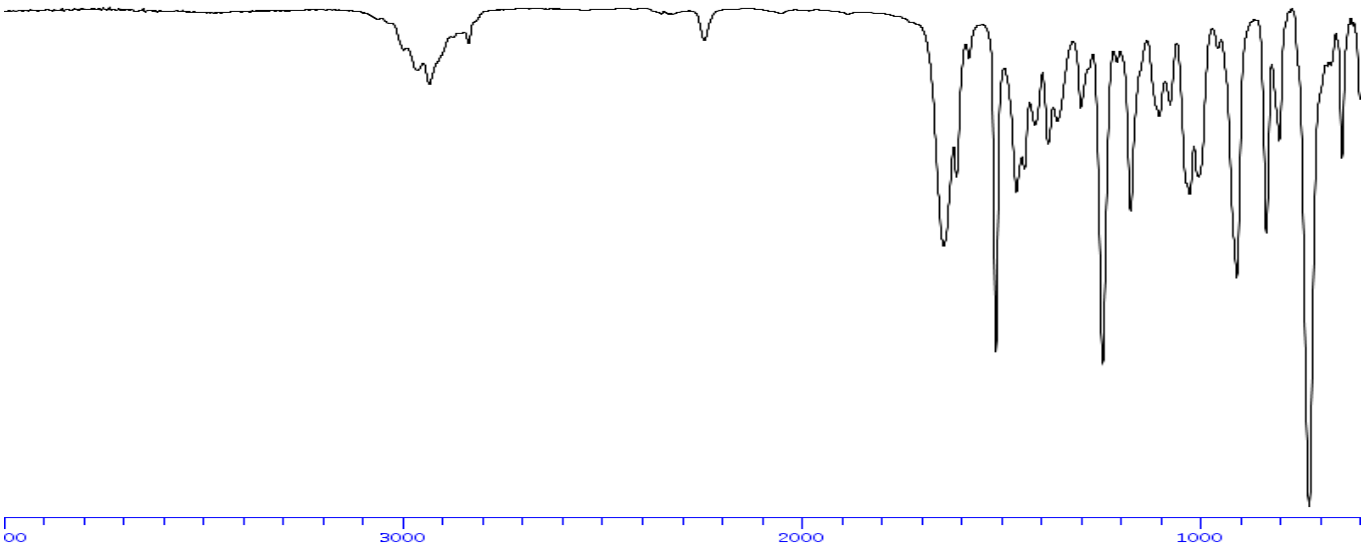
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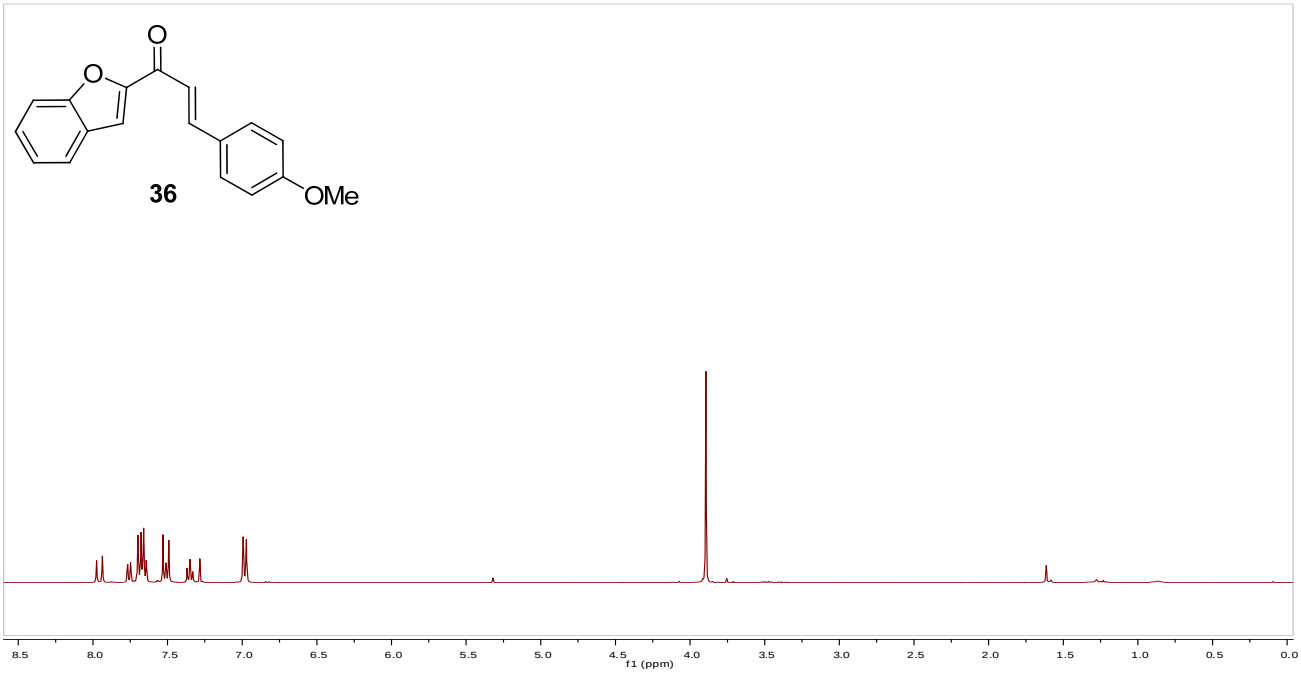
O
O
OMe
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7.0
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6.0
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3.5
3.0
2.5
2.0
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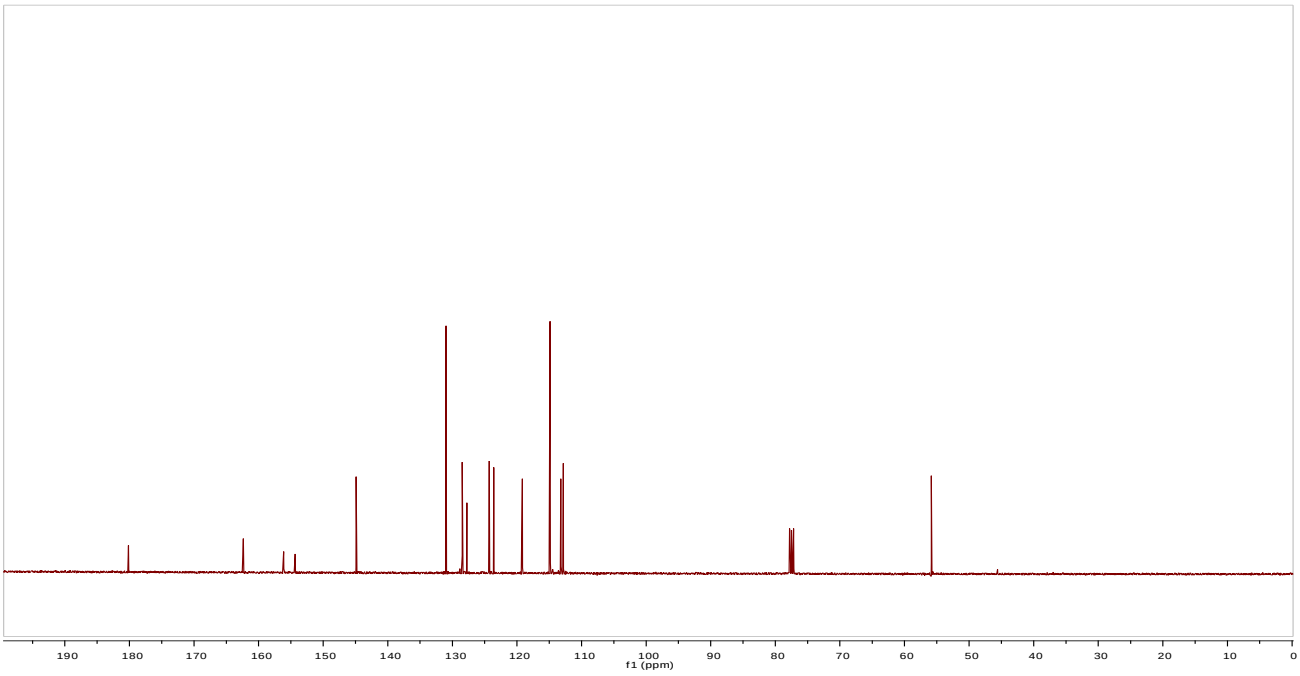
1.0
0.5
0.0
f1 (ppm)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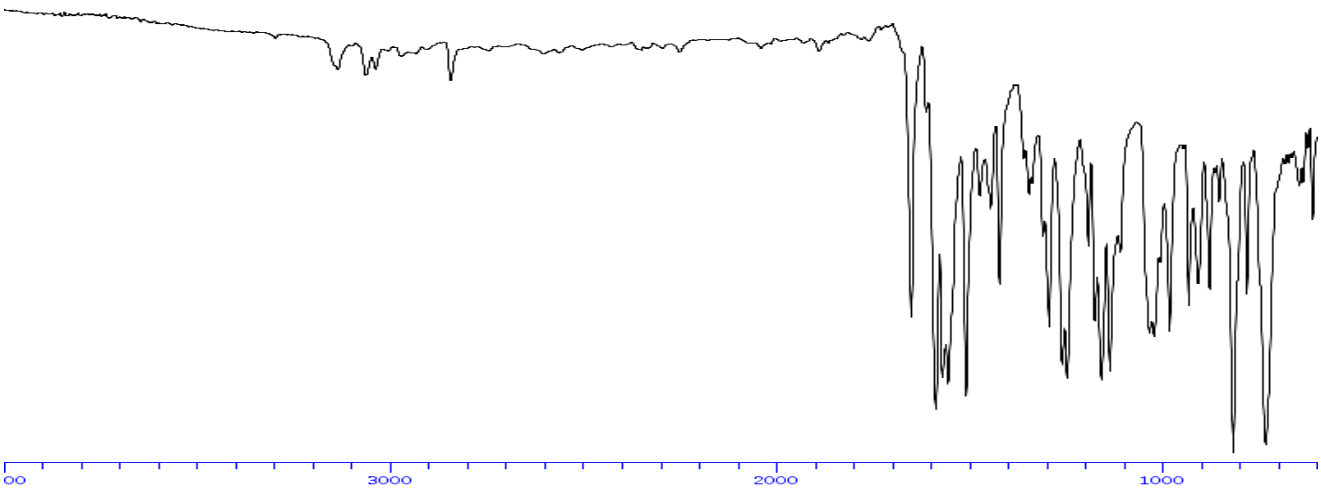
f1 (ppm)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2000
1000